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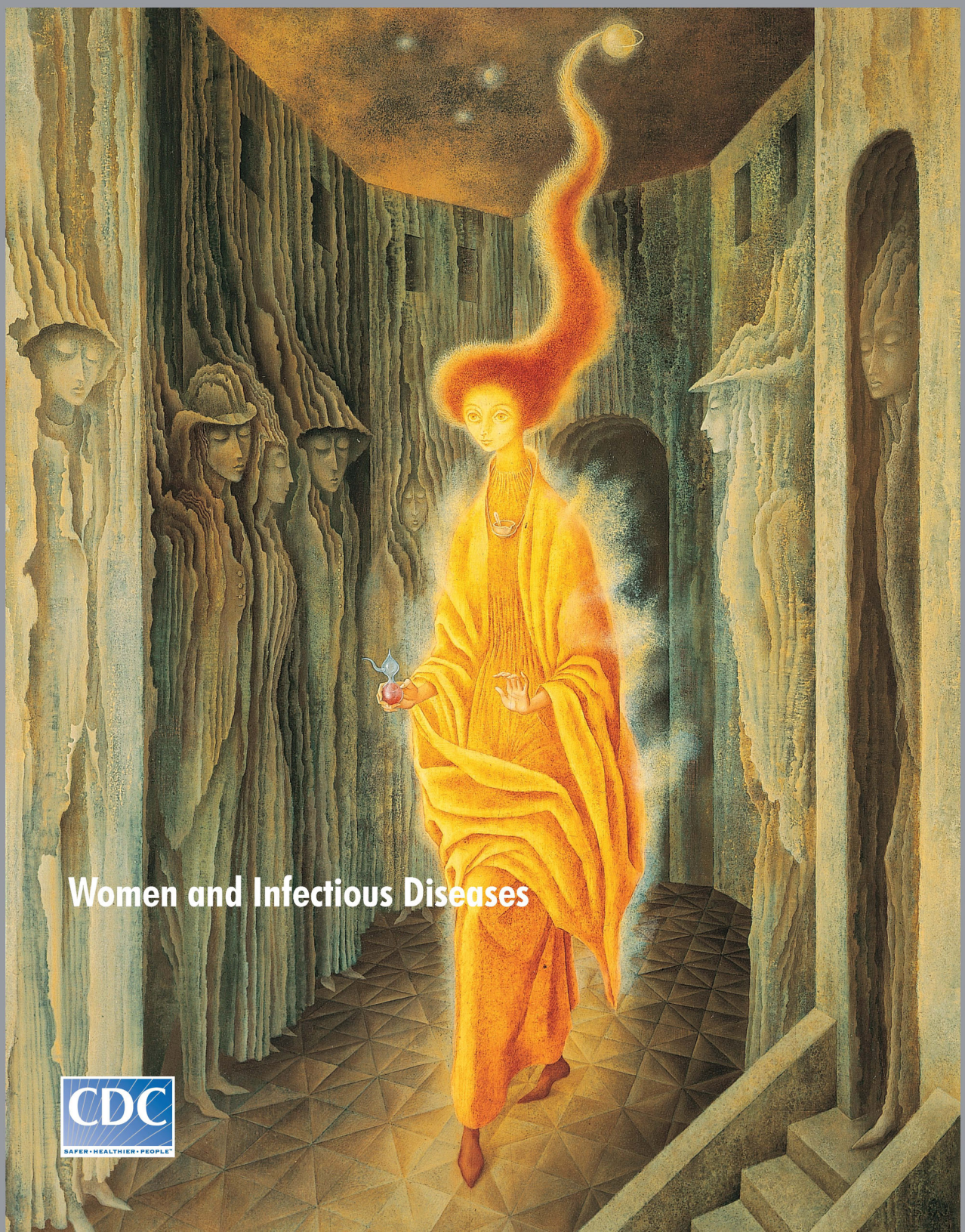

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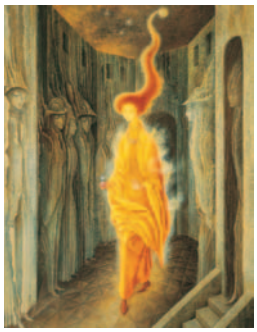

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Remedios Varo (1908–1963)
La Llamada (The Call) (1961)
Oil on Masonite (98.5 cm x 68 cm)
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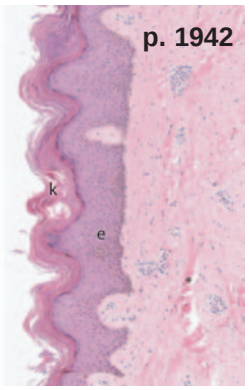

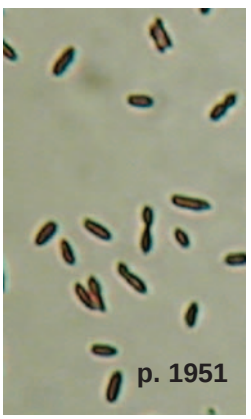

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International Conference on Women and Infectious Diseases

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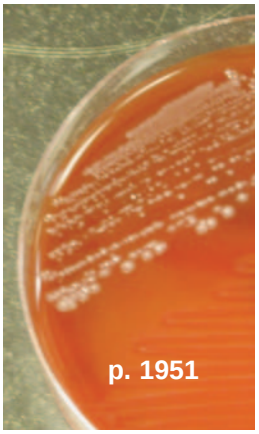
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Trachoma Decline and Widespread Use of Antimicrobial Drugs

Jaya D. Chidambaram,* Mariko Bird,* Vivian Schiedler,* Alicia M. Fry,† Travis Porco,‡ Ramesh C. Bhatta,§ Hem Jha,§ J.S.P. Chaudary,§ Bruce Gaynor,* Elizabeth Yi,* John P. Whitcher,* Susie Osaki-Holm,* and Thomas M. Lietman*

Trachoma is disappearing in many parts of the world, even in the absence of specific control programs. Following mass antimicrobial drug treatments for trachoma in western Nepal, the prevalence of trachoma declined far more rapidly than could be attributed to the control program alone. Pharmacy surveys in the same region found that children received more antichlamydial drugs from sources outside the trachoma program than they did from the program itself. We demonstrate that high background antimicrobial drug use may be responsible for much of the observed decline in trachoma and discuss its potential role in eliminating this infectious disease.

Trachoma is disappearing in many parts of the world, even in the absence of specific control programs. It is a disease of the rural poor, and as living conditions have improved during the last century, a corresponding decline in trachoma has occurred (1–4). In Western Europe and the United States, trachoma virtually disappeared by the late 20th century. Other infectious diseases such as syphilis, chancroid, tuberculosis, and leprosy also began to subside in Europe and the United States during this time. This downward trend seems to have begun before, and continued into, the antimicrobial drug age. Therefore, many attribute this decline to socioeconomic factors, such as improved sanitation and social changes, and even to legislation to control venereal disease, rather than to antimicrobial drugs. Addressing the importance of antimicrobial agents in the disappearance of these infectious diseases retrospectively is difficult. In the case of trachoma, we have a unique opportunity to observe the effect of rising antimicrobial pressure in the community on a disease that is in decline but has not yet disappeared.

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From 1998 to 2001, a region of western Nepal was monitored for trachoma prevalence, following mass antimicrobial drug distribution for trachoma. A dramatic fall in disease prevalence was observed that could not be attributed to the effect of the trachoma control program alone (5). We conducted a survey of pharmacies in the same region and found a surprisingly large quantity of antimicrobial drugs were being used for indications other than trachoma control (6). Here, we evaluate whether this background antimicrobial use may be responsible for the downward secular trend in the prevalence of trachoma.

Analysis of Decline in Trachoma Prevalence in Western Nepal

From May 1998 to May 2001, a total of 25 villages from three subdistricts (known as Village Development Committees) in the Kailali and Konchapur districts of far-western Nepal were monitored for clinically active trachoma. During this time, an annual mass azithromycin treatment program began. At each visit, all children 1–10 years of age were examined for signs of clinically active trachoma by using the World Health Organization (7) simplified trachoma grading system (8). In total, >20,000 examinations were performed; 180–650 children were examined during each village visit (5). The presence of a secular trend, a downward trend independent of the trachoma program, was evaluated by monitoring one third of the villages for 6 months before any antimicrobial drug treatment was given. Seasonal variation was determined by performing village visits in both the spring and the fall. No other specific trachoma prevention activities such as hygiene, fly control, or water supply programs were instituted during the course of this study (9).

Trachoma prevalence data were analyzed by using a multivariate autoregression (AR1) model with the following covariates: effect of the trachoma program, seasonal variation, and secular trend. The analysis showed that the

trachoma program's distributions of antimicrobial drugs alone could account for some, but not all, of the observed reduction in clinically active trachoma (5). A substantial proportion of the decrease in trachoma prevalence 6 months posttreatment was attributable to a secular trend, independent of the trachoma program's effect and seasonal changes (26% decrease, $p < 0.001$, 95% confidence interval [CI] 15%–35% decrease).

Antimicrobial Pressure from Outside the Trachoma Program

From February to May 2000, all pharmacies and government health posts in the Geta subdistrict of Kailali were surveyed to establish the total quantity of antimicrobial drugs distributed. All of these will be called pharmacies for the purposes of this article. Information obtained included the number of years each medicine hall had been open and, for each patient, age, antimicrobial agent, amount distributed, and patient's village. Pharmacy purchase receipts from this time period were also collected for analysis. The survey was repeated in September 2001 to gain additional patient information and to ensure that no gross seasonal variations occurred (6).

We analyzed these data to determine what percentage of the total antimicrobial agents distributed had antichlamydial activity. Susceptibility testing suggested that trimethoprim-sulfonamide combinations, tetracycline, macrolides, chloramphenicol, and amoxicillin are all effective against chlamydia. Also, other penicillins, cephalosporins, and the fluoroquinolones (ciprofloxacin and norfloxacin) are less effective antichlamydial agents (10). However, susceptibility testing for chlamydia has been difficult to standardize (11), and alternative assumptions could alter these percentages somewhat. For example, including ciprofloxacin, which has some effect against *Chlamydia trachomatis*, would have increased the proportion effective against chlamydia by 12%, but we used the lower, more conservative figure for analysis. To facilitate direct comparison of different antimicrobial agents, the total amount of antichlamydial antimicrobial drugs was converted into the standardized unit of defined daily doses (DDD). DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (12). For children, the number of prescriptions given per child per year was calculated with 1998 census data. Both DDDs and the prescriptions per person-year are convenient measures to compare antimicrobial pressure, although neither is ideal; DDDs do not take into account the duration of each drug's antichlamydial activity, and prescriptions are not for a uniform amount of medication.

We estimated that pharmacies in Geta distributed 3.0 DDD of antimicrobial drugs per person per year in 2000 (Table). Sixty-eight percent of these prescriptions were effective against chlamydia (Figure 1). Thus, pharmacies distributed 2.0 DDD per person per year of antichlamydial agents. Forty-nine percent of all antimicrobial agents were distributed to children 0–10 years of age, and 33% to preschool children 0–5 years of age. We estimated that on average 1.2 prescriptions of antichlamydial agent are given to each preschool child per year (Table).

The number of pharmacies in Geta subdistrict has increased from 2 to 14 within the last 20 years, coinciding with the decrease in trachoma prevalence in the Tarai region of Nepal (Figure 2) (2). Eight of these pharmacies (57%) have been open for ≤5 years, and 10 (71%) for ≤10 years. In the last 20 years, the number of pharmacies has increased sevenfold, while the population of Geta has grown by approximately twofold, which suggests that more than three times as many pharmacies exist per person currently than in 1980.

Antimicrobial Drug Use within the Trachoma Program

The trachoma control program in Kailali and Konchapur distributed single-dose oral azithromycin annually, as per World Health Organization (WHO) guidelines and covered an estimated 80% of the targeted population with its antimicrobial treatments (5,9). One gram of azithromycin is the recommended single dose in an adult to treat ocular chlamydial infection. This dose is equivalent to 3.3 DDD/person (12). For children, the recommended single dose of azithromycin is 20 mg/kg. The average dose for all

Table. Comparison of antimicrobial drug use within and outside a trachoma program[a]

	DDD/person/year to all ages	Prescriptions/person/year to preschool children
Antimicrobial pressure from pharmacies		
All antimicrobial drug prescriptions (from survey)	3.0	1.8
Antichlamydial prescriptions (from survey)	2.0	1.2
Antimicrobial pressure from trachoma program		
Annual azithromycin treatment with 100% coverage (theoretical)	2.3	1
Annual azithromycin treatment with 80% coverage (theoretical)	1.9	0.8

[a]Pharmacy survey data showing the total quantity of antimicrobial drugs used in Geta subdistrict and the proportion of antimicrobial drug with antichlamydial activity. An annual trachoma program theoretically gives 1 g of azithromycin to every adult (3.3 DDDs) and a lower dosage to children, averaging approximately 2.3 DDDs per person for all ages. We estimate from a mathematical model that mass antimicrobial treatment every 1.7 years would be sufficient to eventually eliminate ocular chlamydial infection from this region (13). DDD, defined daily dose, the average adult daily dosage for a drug's primary indication.

ages (adults and children) was found to be approximately 2.3 DDD/person (9). With a treatment coverage of 80% of the entire population as recommended by WHO, a trachoma program would therefore administer 1.8 DDD/person at each mass distribution of antimicrobial agents.

Antimicrobial Drug Use Necessary for Elimination of Trachoma in Western Nepal

Using a previously described mathematical model, we estimated the frequency of mass azithromycin distributions and the amount of antimicrobial drug needed to eliminate infection from this region of western Nepal (13). Before treatment, the average prevalence of active trachoma was 17% in children 1–10 years of age in western Nepal (5). With antimicrobial drug treatment that is 95% effective in a person and with 80% coverage of the population, the model indicates that mass treatments would be needed every 1.7 years (20.4 months) in western Nepal to progressively reduce the prevalence of active trachoma. Therefore, mass treatments given annually would be more than enough to eliminate ocular chlamydial infection.

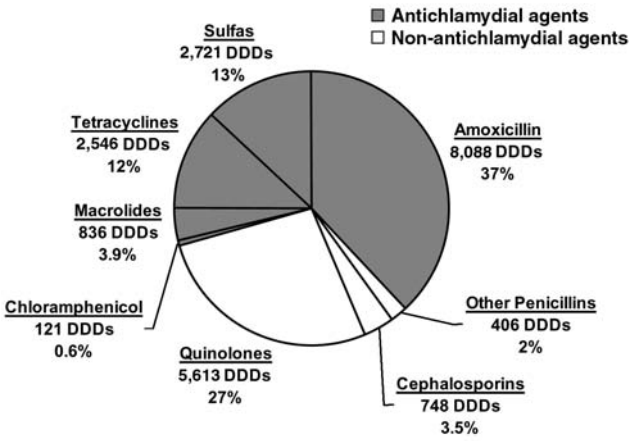

Figure 1. Antimicrobial drug use in Geta, Nepal. Antimicrobial drug sales in a 3-month period (mid-February to mid-May 2000) from all pharmacies in the Geta subdistrict, expressed as defined daily doses (DDDs) and as a percentage of the total DDDs sold (6). The shaded region represents antimicrobial drugs that are effective against *Chylmydia trachomatis*.

Discussion

The amount of antichlamydial drugs given out by pharmacies in Geta (2.0 DDD/person/year) is slightly more than the estimated amount that would bring about the elimination of ocular chlamydial infection in this region of western Nepal (1.9 DDD/person/year). Children, in particular preschool children, are by far the most likely to harbor ocular chlamydia. Pharmacies distributed nearly one half of the total antimicrobial agents to children 0–10 years of age, and one third to children 0–5 years of age. Preschool children received 1.2 prescriptions per year of antimicrobial drugs that are effective against chlamydia, which is far more than the estimated 0.6 per year that would eliminate infection. We therefore conclude that antibiotics given for reasons other than trachoma control may play a role in the disappearance of trachoma in this region.

The prevalence of active trachoma has decreased in many regions of the world in the absence of programs specifically targeting this disease (1–4,14,15). From 1981 to 1996, active trachoma in children declined from 30% to <10% in each of two adjacent districts of western Nepal; one district had an intense trachoma control program; the other district did not (2). Surveys in the Kailali and Konchapur districts of western Nepal have shown a large secular trend, suggesting that active trachoma would have disappeared rapidly even if a trachoma program had not been implemented (5). This situation is not unique to Nepal. A village in Gambia had hyperendemic trachoma in 1959 (66% prevalence in children), yet a followup survey in 1987 found that active disease had nearly disappeared, after only a modest 2-year control program of tetracycline administration (1). A study in Malawi showed a 50% reduction in active trachoma over a 16-year period in the absence of a specific trachoma program (4).

What might be the cause of this secular trend seen in so many countries? Various socioeconomic factors have been associated with the disappearance of trachoma, but studies have had difficulty establishing causality for any of them (16–18). In particular, facial hygiene and fly density are both believed to be related to trachoma activity (19–21). Several studies have associated dirty faces with active trachoma (22,23), but a trial involving intensive face-washing produced a modest (and statistically insignificant) decrease in clinically active trachoma at 1 year (21). The face fly (*Musca sorbens*) has been implicated as a vector of trachoma (24,25). A recent study in the Gambia found that regular insecticide spraying in villages did reduce active trachoma (25); however, future controlled studies are necessary to determine the sustainability of this promising measure.

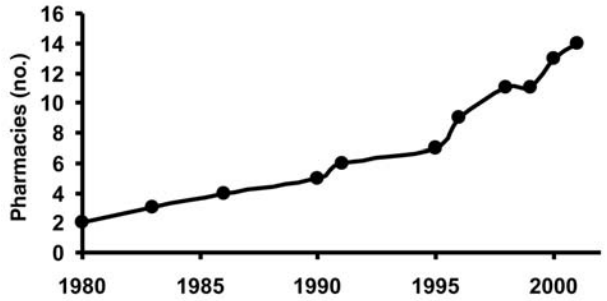

Figure 2. Number of pharmacies in Geta, Nepal. The number of pharmacies in Geta subdistrict increased from 2 in 1980 to 14 in 2001.

What role have antimicrobial agents played in the disappearance of trachoma? In a person, ocular chlamydial infection can be successfully treated with a single dose of azithromycin (26,27). At the community level, controlled trials in Tanzania, Gambia, and Egypt have shown that a single course of azithromycin can markedly reduce ocular chlamydial infection, even 1 year later (28). Our findings in this study support the hypothesis that the rising use of antimicrobial drugs in the community for indications other than trachoma may contribute to the disappearance of this disease.

Several of the principal antimicrobial drugs used in Nepal for systemic infectious diseases have antichlamydial action. National treatment guidelines for childhood pneumonia recommend co-trimoxazole (a combined preparation of sulfonamide and trimethoprim) as the treatment of choice, followed by amoxicillin or oral chloramphenicol as second-line therapy (29). Other childhood infectious diseases are treated according to the adapted WHO Integrated Management of Childhood Illness (30). WHO recommends chloroquine as the first-line therapy for malaria in Nepal, and sulfadoxine-pyrimethamine for chloroquine-resistant cases (31). The latter drug has antichlamydial activity through its sulfonamide component, sulfadoxine.

Why trachoma is disappearing should be investigated before it is gone, so that this knowledge can be applied to other diseases. If infection in a region is already in decline, the effect attributed to a trachoma control program may be exaggerated, and the program's success may not be duplicated in less fortunate areas. Conversely, beneficial factors could be introduced in areas where a downward secular trend does not already exist. Much discussion has taken place about the dangers associated with the indiscriminate use of antimicrobial drugs. These problems should be balanced against the benefits. The widespread use of antimicrobial drugs in developing countries for indications other than trachoma may play a role in eradicating one of the world's leading causes of preventable blindness.

Acknowledgments

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Public Health Interventions and SARS Spread, 2003

David M. Bell* and World Health Organization Working Group on Prevention of International and Community Transmission of SARS[1]

The 2003 outbreak of severe acute respiratory syndrome (SARS) was contained largely through traditional public health interventions, such as finding and isolating case-patients, quarantining close contacts, and enhanced infection control. The independent effectiveness of measures to "increase social distance" and wearing masks in public places requires further evaluation. Limited data exist on the effectiveness of providing health information to travelers. Entry screening of travelers through health declarations or thermal scanning at international borders had little documented effect on detecting SARS cases; exit screening appeared slightly more effective. The value of border screening in deterring travel by ill persons and in building public confidence remains unquantified. Interventions to control global epidemics should be based on expert advice from the World Health Organization and national authorities. In the case of SARS, interventions at a country's borders should not detract from efforts to identify and isolate infected persons within the country, monitor or quarantine their contacts, and strengthen infection control in healthcare settings.

The 2003 outbreak of severe acute respiratory syndrome (SARS) is a modern example of containing a global epidemic through traditional or nonmedical public health interventions. The interventions included finding and isolating case-patients; quarantining contacts; measures to "increase social distance," such as canceling mass gatherings and closing schools; recommending that the public augment personal hygiene and wear masks; and limiting the spread of infection by domestic and international travelers, by issuing travel advisories and screening travelers at borders. Some measures were implemented pursuant to recommendations of the World Health Organization (WHO); others were implemented by governments on their own initiative. A novel technology, infrared scanning, was used extensively in some countries to try to identify persons with fever at international borders and in public places. After the outbreaks, WHO sought information to help assess the effectiveness of interventions in preventing the transmission of SARS in the community and internationally. Of particular interest was information on the effectiveness of thermal scanning of travelers.

Methods

Information was obtained by reviewing scientific literature and surveying members of an informal WHO working group about preventing community and international transmission of SARS. Members were surveyed with standardized questionnaires regarding measures taken in their countries and evaluation studies known to them.

*World Health Organization, Geneva, Switzerland

[1]The members of the World Health Organization (WHO) Working Group are as follows: Ximena Aguilera, Ministerio de Salud, Santiago Chile; Roy Anderson, Imperial College London, United Kingdom; Dounia Bitar, Institut de Veille Sanitaire, Paris France; Martin Cetron (with Pattie Simone), Centers for Disease Control and Prevention, Atlanta, Georgia, USA; Chew Suok Kai (with Benjamin K.W. Koh), Ministry of Health, Singapore; Clete DiGiovanni, Jr., Defense Threat Reduction Agency, Fort Belvoir, Virginia, USA; Arlene King, Health Canada, Ottawa, Canada; Cindy K-L Lai (with P.L. Ma), Department of Health, Hong Kong Special Administrative Region, China; Angus Nicoll (with Jane Leese), Communicable Disease Surveillance Centre, London, United Kingdom; Sonja Olsen, International Emerging Infections Program, Nonthaburi, Thailand; Alice Sarradet, Direction Generale de la Sante, Paris, France; Mingchang Song, General Administration of Quality Supervision, Inspection and Quarantine, (AQSIQ), Beijing, China; Ron St. John (with Susan Courage), Health Canada, Ottawa, Canada; Robert Steffen (with Leonie Prasad), University of Zurich, Switzerland; Ih-Jen Su (with S.K. Lai), Taiwan Center for Disease Control, Taipei, Taiwan, China; WHO Staff in the Department of Communicable Diseases Surveillance and Response (CSR): Julie Hall, Beijing, China; Emmanuel Jesuthasan, Angela Merianos, Cathy Roth, Max Hardiman, Geneva, Switzerland; Hitoshi Oshitani, Western Pacific Regional Office, Manila, Philippines; and group facilitator: David Bell, WHO (CSR) Geneva, Switzerland, and Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Preventing transmission in healthcare settings was not addressed but had a major impact on preventing the transmission of SARS into the community and internationally (1,2).

Results

Local and National Interventions

Identifying Patients and Quarantining Contacts

Ascertaining and isolating case-patients, combined with rapid identification and management of contacts, were highly effective in interrupting transmission in several countries (1–6).[2] For example, a study in Singapore demonstrated a correlation between rapidly isolating patients after onset of symptoms and a decreased number of secondary cases among their contacts (4) (Figure). Contacts in these countries were placed in various forms of quarantine or, less commonly, monitored for symptoms without confinement and isolated if and when symptoms emerged. The location of quarantine was usually at home but was sometimes at a designated residential facility (e.g., for travelers, persons who did not wish to remain at home for fear of exposing their families, homeless persons, and noncompliant persons). In some cases, quarantined persons were allowed to leave the quarantine site with the permission of local health authorities if they wore masks and did not use public transportation or visit crowded public places. In at least one area, these restrictions were applied to essential workers and termed "work quarantine."

Several respondents emphasized that the modern concept of quarantine differs greatly from quarantine in past centuries. Quarantine is most acceptable and arguably most effective when protecting the health and rights of quarantined persons is emphasized. In previous centuries, sick and exposed persons were often locked up together and received limited medical care. Moreover, quarantine was sometimes applied in an arbitrary and discriminatory fashion, targeting lower socioeconomic classes and racial minorities. The modern concept emphasizes science-based interventions with attention to the medical, material, and mental health needs of quarantined persons and protecting fundamental human rights. Exposed persons who are not sick should be separated from symptomatic patients, monitored for the minimum time necessary (e.g., one maximum incubation period), and provided appropriate medical care at the first sign of illness during the monitoring period. Quarantine may be applied to individual persons, to small groups, or, in extreme cases, to entire neighborhoods or other geographic districts ("cordon sanitaire") (7,8).

In the SARS epidemic, persons under quarantine were mostly confined at home and actively monitored for symptoms. In several countries, quarantine was legally mandated and monitored by neighborhood support groups, police and other workers, or video cameras in homes. In other areas, compliance was "requested," but court orders were issued for a small percentage of noncompliant persons. Reports indicate that SARS was diagnosed in 0.22% of quarantined contacts in China-Taiwan, 2.7% in China-Hong Kong Special Administrative Region (SAR), and 3.8%–6.3% in China-Beijing. These different rates were partly due to different criteria for placing persons in quarantine. Contacts at highest risk (aside from healthcare workers with certain unprotected patient care exposures) had been exposed to ill family members (6,9–11).

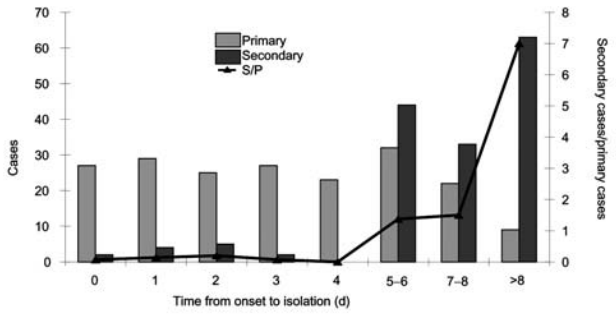

Figure. Severe acute respiratory syndrome cases in Singapore, February 25–May 5, 2003. Number of primary cases (gray) by time from symptom onset to isolation, number of secondary cases infected by such cases (black), and mean number of secondary cases per primary case. Reprinted with permission from Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Science 2003;300:1966–70. Copyright 2003 by the American Association for the Advancement of Science. http://www.sciencemag.org

Quarantine led to financial and psychosocial stresses, risk communication, compensation, and workforce staffing issues for persons, families, employers, and governments. Legal appeals and defiance of quarantine orders were rare (2,6,8–13).

The optimal management of contacts, stratified according to risk of becoming ill, remains under discussion in several countries, e.g., whether confinement is always needed or close monitoring of health status without confinement would suffice. Reports from Canada indicate that the insidious onset of symptoms sometimes posed challenges for clinicians and public health officials. "Timely diagnosis and isolation of cases were sometimes hindered by delays in patient recognition of symptoms, obtaining medical evaluation, and/or physician recognition of the significance of symptoms, which occasionally waxed and waned early in illness" (A. McGeer and D. Low, Mount Sinai Hospital Toronto, pers. comm.). "In Toronto, some

[2]The term "isolation" is applied to ill persons; "quarantine" is applied to persons who have been exposed but are not ill.

healthcare workers continued to work without recognizing that they were ill, perhaps confusing their symptoms with fatigue, despite daily screening and repeated messages not to come to work if ill. This resulted in transmission to patients and staff" (B. Henry, Toronto Public Health, pers. comm.).

Measures To Decrease Time from Symptom Onset to Isolation of Patients

Public campaigns to accelerate reporting and evaluating symptomatic patients appeared to decrease the interval between onset of symptoms and isolation of ill patients in several areas (3,4). Novel interventions included urging the entire population of affected areas to measure their temperature at least once daily, fever telephone hotlines (14), and fever evaluation clinics with appropriate infection control measures. Thermal scanning in public places was implemented in several areas where community transmission was suspected. Data on the effectiveness of this practice are not available, but in Beijing thermal screening was not an efficient way to detect cases among intercity travelers (5).

Measures To Increase Social Distance

Measures to increase social distance, e.g., canceling mass gatherings; closing schools, theaters, and public facilities; and requiring masks for all persons using public transport, working in restaurants, or entering hospitals, were implemented in areas where extensive unlinked community transmission of SARS coronavirus (SARS-CoV) was suspected. Many persons in these areas also chose to wear masks outside their homes. These measures were often applied simultaneously with other measures, including enhanced contact tracing, which makes their independent effectiveness difficult to assess. However the simultaneous introduction of a variety of measures was temporally associated with dramatic declines in new SARS cases. A case-control study in Beijing found that wearing a mask more frequently in public places may have been associated with increasing protection (15). Another case-control study in China-Hong Kong found that using a mask "frequently" in public places, washing one's hands >10 times per day, and "disinfecting living quarters thoroughly" appeared to be protective (16). The types of masks used were not specified. With the exception of the Amoy Gardens cluster in which SARS-CoV was apparently transmitted through accidentally produced aerosols of sewage (17), SARS transmission in the community from aerosols or in social settings appeared to be rare.

Disinfection

In some areas, disinfectants were applied inside the homes and vehicles of persons with SARS, ambulance tires, and pedestrian walking zones. Little information exists on the effectiveness of disinfectant use in reducing community or hospital transmission. In Hong Kong, disinfecting living quarters thoroughly (not otherwise defined and reported retrospectively by telephone) appeared to be protective (16).

Measures for International Travel

Travel Advisories

Travel advisories (e.g., advice to postpone nonessential travel) were issued by WHO and various governments. Air travel to areas affected by the advisories decreased dramatically during the epidemic (M.A. Hinayon and D. Gamper, Airports Council International, communication to WHO), although the impact of advisories compared with other sources of information to travelers, such as news media reports of SARS cases, is difficult to assess.

Measures for International Borders

Passive and active methods were used to provide information and screen entering and exiting travelers. These methods included signs, videos, public address announcements, distributing health alert notices, administering questionnaires to assess symptoms and possible exposure, visual inspection to detect symptoms, and thermal scanning.

Few data exist on the relative effectiveness of methods of providing information to travelers. Available data on the effectiveness of screening and other measures directed to travelers are sometimes difficult to interpret because they may not distinguish between entry and exit screening, specify how many entering travelers were from affected countries, distinguish the epidemic period from subsequent, or include the number of SARS cases detected.

Health Alert Notices to Entering Travelers

Combined data from Canada, China (mainland, Hong Kong SAR, and Taiwan), France, Singapore, Switzerland, Thailand, and the United States indicate that approximately 31 million travelers entering these countries received health alert notices. Of these, approximately 1.8 million were reported as arriving from affected areas; this estimate is likely low given the difficulties in tracking travelers and the fact that many airline passengers change planes en route. Inadequate data exist to evaluate the effect of distribution of most of these notices. China-mainland reported distributing 450,000 notices and detecting four SARS cases that may have been linked to the notices (M. Song, China Dept of Health and Quarantine Supervision and Management, communication to WHO). Thailand printed l million notices; as a result 113 cases of illness (108 at airports, l at a seaport, and 4 at land crossings) were detected. Twenty-four cases were suspected or probable SARS: all of which

were detected at airports (S. Warintrawat, Ministry of Public Health, Thailand, communication to WHO).

Entry Screening

Preliminary data from a worldwide survey indicate that among 72 patients with imported probable or confirmed SARS cases, 30 (42%) had onset of symptoms before or on the same day as entry into the country and symptoms developed in 42 patients (58%) after entry (J. Jones, United Kingdom Health Protection Agency, communication to WHO). SARS was diagnosed in a small percentage of persons who completed entry health declaration questionnaires in affected areas during the SARS epidemic. (Table 1).

Results combined from Canada, China (including the mainland and Hong Kong SAR), and Singapore indicate that no cases of SARS were detected by thermal scanning among >35 million international travelers scanned at entry during the SARS epidemic (Table 2; data for China-Hong Kong SAR include travelers arriving from China-mainland). Temperature screening of 13,839,500 travelers entering or leaving Beijing by air, train, or automobile identified 5,097 patients with fever, of whom 12 had probable SARS. These 12 included 10 of 952,200 domestic airline passengers and 2 of 5,246,100 train passengers. None of 275,600 international travelers who underwent temperature screening had SARS (5).

In China-Taiwan, incoming travelers from affected areas were quarantined; probable or suspected SARS was diagnosed in 21 (0.03%) of 80,813. None of these 21 was detected by thermal scanning when they entered China-Taiwan (9) (S.K. Lai, China-Taiwan Center for Disease Control, pers. comm.).

Exit Screening

After WHO recommended exit screening on March 27, 2003 (18), no additional cases from airline travel were documented from countries with screening. Combined data from China (Hong Kong SAR and Taiwan) indicate that among 1.8 million people who completed health questionnaires at exit, 1 probable case of SARS was detected. Combined data from Canada, China (Hong Kong SAR and Taiwan), and Singapore indicate that no cases of SARS were detected among >7 million people who underwent thermal scanning at exit (Table 3) (S. Courage, Health Canada, S.K. Lai, China-Taiwan Center for Disease Control; P.L. Ma, Hong Kong SAR China Dept of Health; and B.K.W. Koh, Singapore Ministry of Health, communications to WHO). In some areas, "stop lists" were used at borders to prevent persons on isolation or quarantine lists from exiting. Anecdotes suggest that exit screening may have helped dissuade ill persons from traveling by air but may have been more successful in dissuading local residents from traveling abroad than in dissuading ill travelers from attempting to return home.

Transmission on Commercial Aircraft

Five commercial international flights were associated with transmission of SARS from patients with symptomatic probable cases to passengers and crew (1). Notification of exposed passengers and studies of transmission risk were greatly hampered by difficulties in identifying and tracing passenger contacts (19–23). In the most comprehensive investigation, involving three flights with extensive passenger tracing and laboratory confirmation of index and secondary cases, a wide range of risk was noted (Table 4). For flight 2, in which the secondary attack rate was 18.3%, the risk of infection was increased for persons seated close to the index patient, but most passengers who became infected were seated farther away, even though their individual risk was lower (19). In another study, one person with SARS, who had difficulty breathing but was not coughing, infected two other passengers. One of these sat in the row in front of the index patient but the other passenger sat four rows, plus a passageway, behind and on the opposite side of the plane (20). On nine flights arriving in Singapore, the incidence of transmission from passengers with SARS who had respiratory symptoms was estimated at 1 in 156 persons (21). A fourth study found no transmission to passengers seated near a patient who took multiple flights (22). In comparison, an influenzalike illness developed within 3 days in 72% of passengers in a plane containing a person with symptomatic influenza and grounded for 3 hours without ventilation (24). The risk for transmission

Table 1. Health declarations by entering travelers at international borders, March 1–July 15, 2003[a]

Area	No. completed declarations (millions)	No. reporting symptoms	No. reporting contact with SARS	No. with SARS detected by declarations
Canada	10	3,481	0	0
China-mainland	13.2	2,035	500	2 (both had SARS contact)
China-Hong Kong SAR[b]	19.3	2,380	NA	2 (both had symptoms)
China-Taiwan	1.0	5,287	NA	0
Singapore	1.9	Very low	0	0
Total	45.4	13,000	500	4

[a]SARS, severe acute respiratory syndrome; SAR, special administrative region.
[b]Includes border between China-Hong Kong SAR and China-mainland.

Table 2. Thermal scanning of entering travelers at international borders, March 1–July 15, 2003[a]

Area	No. scanned (millions)	No. febrile by scan (confirmed orally)	No. SARS found by scanning
Canada	0.6	248 (215)	0
China-mainland	13.0	4,070 (351)	0
China-Hong Kong SAR[b]	15.1	NA (451)	0
China-Taiwan	1.0	1,211 (0)	0
Singapore	6.0	5,200 (3,160)	0
Total	35.7	10,729 (4,177)	0

[a]SARS, severe acute respiratory syndrome; SAR, special administrative region.
[b]Includes border between China-Hong Kong SAR and China-mainland.

of tuberculosis during a long flight was also increased among, but not limited to, passengers seated close to a highly infectious index patient (25).

Discussion

SARS-CoV was contained in human populations in 2003 largely by aggressive use of traditional public health interventions (case finding and isolation, quarantine of close contacts, and enhanced infection control measures in settings where care was provided to persons with SARS, especially in healthcare facilities and homes). These measures also contained a smaller SARS outbreak in 2004 that originated from a laboratory-acquired infection (26). Measures to decrease the interval between onset of symptoms and isolation were effective in containing community transmission. The independent effectiveness of general community measures to increase social distance (in addition to contact tracing and quarantine) and improve hygiene and wearing masks in public places requires further evaluation.

Limited information exists on the relative effectiveness of methods of providing information on SARS (or other illnesses) to travelers. For inbound travelers who may have been exposed to SARS, such information should include what to do if symptoms develop and the need to inform healthcare workers who provide care for them in advance to take appropriate precautions. Entry screening of travelers by using health declarations or thermal scanning at international borders had little documented impact in detecting SARS cases. Exit screening appeared only slightly more effective; however, the possible value of these interventions in deterring travel by ill persons and building public and business confidence was not assessed. Preventing passengers with SARS from boarding aircraft would likely have reduced transmission of infection, but the most cost-effective ways to accomplish this are uncertain. The difficulties in identifying and tracing passengers exposed on aircraft highlight the need for public health authorities to have a mechanism for rapid access to passenger contact information. In the case of SARS, the data on border screening indicate that if resources are limited, interventions at a country's international borders should not detract from efforts to identify and isolate infected persons within the country, monitor and quarantine their close contacts appropriately, and strengthen infection control in healthcare settings.

In retrospect, although SARS-CoV was transmitted primarily through the respiratory droplet route, certain epidemiologic parameters facilitated its containment through public health interventions . Presymptomatic transmission was not observed. Infectivity in most patients was low at onset of illness and seemed to peak during week 2 of illness in association with maximal respiratory symptoms, when patients were often in the hospital. Virus transmission was primarily by respiratory droplets, with little natural airborne dissemination but some environmental spread. With some important exceptions (Hotel M and Amoy Gardens in Hong Kong), transmission occurred primarily in healthcare or household settings, with close person-to-person contact. Cases among children were uncommon, and children did not seem to be involved in transmission. Although the reproductive number for SARS (R_0, the average number of new cases resulting from a single infection in a susceptible community) was approximately 2–4, contact tracing was facilitated by its relatively long serial interval (time between onset of symptoms in successive patients in a chain of transmission: mean 8–10 days) and incubation period (median 4–5 days). Most infections did not lead to further transmission, although a small number of "super-spreading" events occurred in which single

Table 3. Exit screening of travelers at international borders, March 1–July 15, 2003[a]

Area	No. health declarations	No. thermally scanned	No. SARS
Canada	584,819	397,563	0
China-Hong Kong SAR[b]	700,000	2.5 million	0
China-Taiwan	1.1 million	1.0 million	1– by health declaration
Singapore	NA	4 million	0
Total	2.4 million	7.9 million	1– by health declaration

[a]SARS, severe acute respiratory syndrome; SAR, special administrative region.
[b]Includes border between China-Hong Kong SAR and China-mainland.

Table 4. Rates of severe acute respiratory syndrome transmission on commercial aircraft[a]

Flight	Duration	Index patient(s)	No. infected/ no. on plane (%)
1	90 min	1 presymptomatic	0/315 (0.0)
2	3 h	1 fever, cough	22/120 (18.3)
3	90 min	2 fever; 2 fever, cough	1/246 (0.4)

[a]Source: ref 19.

unrecognized cases transmitted to many people, usually in hospitals or households, before appropriate infection control precautions were in place (1).

Traditional public health interventions will likely be required again to combat an emerging or reemerging infection for which specific antimicrobial drug therapy and vaccines are nonexistent or in short supply. For infections that are relatively less transmissible (e. g., SARS or a strain of avian influenza not fully adapted to human-to-human transmission), early and bold use of such interventions may contain transmission. For more readily transmissible infections (e.g., an emerging pandemic strain of influenza), they would not completely halt transmission but might "buy time" during a narrow window of opportunity during which an effective vaccine could be produced and other preparations made. For countries lacking specific countermeasures, such as drugs and vaccines, nonmedical public health interventions may be the only measures available to combat epidemics (27). Decisions regarding implementation should be based on expert scientific advice from WHO and national authorities; the epidemiologic features of the disease and available resources should be taken into account. This article does not address political and economic factors that may lead to calls for adopting certain measures or the economic and social consequences that may ensue, but governments will also consider such factors in their decisions.

The WHO SARS Scientific Research Advisory Committee has identified further research needs for SARS (28). Priorities include evaluating the effectiveness of public health interventions in terms of cases detected, cases prevented, costs, and alleviating public concerns; identifying ways to make quarantines and other restrictions more focused and less burdensome for persons and societies; assessment of how "leaky" restrictions can be before they become ineffective; and developing rapid diagnostic tests. Limitations of the information include that it was collected retrospectively, and in some studies, laboratory testing to confirm SARS-CoV infection was not performed. In the event of future outbreaks, these issues will need to be studied prospectively so that decisions can be based on the best scientific information.

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Topographic Changes in SARS Coronavirus–infected Cells during Late Stages of Infection

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Scanning electron and atomic force microscopy was used for the first time to view the maturation of the severe acute respiratory syndrome–associated coronavirus at the cell surface. The surface form of the cells at advanced infection displayed prolific pseudopodia that, in addition to the rest of the plasma membrane, were also active sites of virus release. High magnification of the maturing virus particles showed a rosette appearance with short knoblike spikes under both the scanning electron and atomic force microscopes. The final expulsion step of the maturing virus particles seemed to result in some disruptions to the plasma membrane. The cytoskeletal network along the edge of the infected cells was enhanced and could be involved in transporting and expelling the progeny virus particles. Thickening of the actin filaments at the cell edge provided the bending force to extrude the virus particles.

A new human coronavirus was identified during the recent outbreak of severe acute respiratory syndrome (SARS) (1–4). The outbreak started during November 2002 in southern China and then spread to Hong Kong, Vietnam, Canada, and Singapore in early 2003. Sequence analyses of various isolates have indicated that the virus is genetically distinct from all known coronaviruses (5–7). Phylogenetic analysis suggests that the SARS-associated coronavirus (SARS-CoV) does not fit in the three currently known groups of coronaviruses (1,5,6,8), which suggests that this is a new virus, not a result of mutation or recombination of known coronaviruses.

Coronavirus infections are common in both domestic animals and humans (9). However, the known human coronaviruses often cause coldlike symptoms, whereas recent infections caused by SARS-CoV do not. The rate of death for SARS infections is 7%–10%, depending on the age of the patients (2).

SARS-CoV grows well in Vero E6 cells (1,2,10) and enters cells by direct fusion of the virus envelope with the plasma membrane (11). The fusion process involving the S glycoprotein is pH independent (12). Once internalized, the virus core uncoats, revealing flattened, disc-shaped, and electron-dense nucleocapsids described as "doughnut-shaped" (10,11). The uncoated nucleocapsids are found within large, smooth, double-membrane vacuoles together with membrane whorls (11). These membrane whorls are postulated to be replication complexes for the virus since they appear very early (within 30 min) after infection. Other reports have described double-membrane vesicles as sites of replication for coronavirus (Linder strain) (13), mouse hepatitis virus (14), and SARS virus (15). The latent period observed was 5–6 h postinfection (10). However, a short latent period is common among coronaviruses (16).

Coronavirus infections can be cytocidal for the cells; or, in some cases, persistent infection can result (17). The outcome of the infection is dependent on the virus strains and cell types. Unlike infection with the hepatitis C virus-229E, wherein virus production can continue for weeks without any expression of cytopathic effects (18,19), infection with SARS-CoV produces copious progeny virus particles within the first 12 h (10). The site of assembly of SARS-CoV was at the Golgi complexes, similar to previous reports for other coronaviruses (20–22). After assembly, the virus progeny particles are transported in vesicles to the cell periphery for release.

The aim of this study was to use scanning electron and atomic force microscopes to investigate changes in the surface topography of SARS-CoV–infected cells at late infection. The results can assist in further understanding how SARS-CoV interacts with infected cells at late infection.

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Thus far, replication studies on SARS-CoV were performed with transmission electron microscopy, which showed detailed intracellular changes during replication in two dimensions. Both scanning electron and atomic force microscopy can provide holistic and three-dimensional views as infection progresses.

Materials and Methods

Cells and Virus

SARS-CoV (2003VA2774) used for this study was isolated from a SARS patient in Singapore by the Department of Pathology, Singapore General Hospital. The virus was grown in Vero E6 cells (ATCC: C1008) in the Environmental Health Institute, National Environmental Agency, Singapore. Infection of the cells grown on coverslips and subsequent fixation (5% glutaraldehyde) of the infected cells at appropriate times were performed at that institute. The microscopy work on the fixed infected cells was performed at the Electron Microscopy Unit, National University of Singapore.

Scanning Electron Microscopy

Vero cells were grown to 70% confluency on sterile glass coverslips in 24-well tissue culture plates before infection with 100 μL of SARS-CoV for 1 h (multiplicity of infection = 10). Maintenance media supplemented with 2% fetal calf serum was added to the wells, and the infected cells were incubated in 37°C incubator with 5% carbon dioxide.

At an appropriate time after infection, the infected cells on the coverslips were fixed with 5% glutaraldehyde overnight. The coverslips were washed with phosphate-buffered saline before being postfixated in 1% osmium tetroxide for 1 h. The coverslips were then washed with distilled water and dehydrated through a series of increasing concentration (25%–100%) of ethanol. Cells on the coverslips were further subjected to critical point drying for 1.5 h and left in a 37°C oven overnight. Subsequently, the cells on the coverslips were sputter coated with gold (thickness of 10 nm) and viewed under the XL30 Field Emission Gun scanning electron microscope (FEI Company, Enidhoven, the Netherlands) at 10 kV.

Atomic Force Microscopy

Infected cells were processed similarly. Normally, samples for the atomic force microscopy should be subjected to minimal processing so that the samples are close to their natural condition. However, in view of the pathogenicity of SARS-CoV, only fixed and gold-coated samples were used for this study. The NanoScope IV MultiMode atomic force microscope was used (Veeco Instruments, Woodbury, NY). Force modulation etched silicon probes were used for imaging (dry TappingMode [Veeco]) infected cells. Hard tapping using appropriate amplitude setpoints was performed with some samples to show subsurface structures.

Negative Staining

Purified virus fixed in 2.5% glutaraldehyde was put onto a formvar carbon-coated grid and allowed to adsorb for a few minutes before being stained with 1% phosphotungstenic acid for 1 min. The excess fluid was blotted and the grid left to dry before viewing under CM120 BioTwin TEM (FEI Company, Enidhoven, the Netherlands).

Results

Both scanning electron and atomic force microscopy showed that the uninfected Vero cells were flat and without prominent form and surface (Figure 1). Pseudopodia, where present, were not extensive (Figure 1A and 1B).

In the transmission electron microscopy studies (10,11,15), SARS-CoV replicated very rapidly and produced large amounts of virus after 6 h of infection. The scanning electron microscopy confirmed that, for some infected cells (15 h postinfection), a large quantity of extracellular virus was present (Figure 2A, arrowheads) on the whole cell surface. However, very few virus particles were on the neighboring cell (top right), indicating a nonsynchronous infection. The scanning electron microscopy images showed a holistic view of SARS-CoV–infected cells compared to ultrathin sections in transmission electron microscopy. Another virus-induced change clearly demonstrated by using the scanning electron microscope was the proliferation of pseudopodia on the infected cells and in particular, at the edge of these cells (Figure 2A, arrows compared to Figure 1).

At higher magnification, progeny virus particles protruded at the cell periphery (Figure 2B, arrow). In the inset (boxed area), a virus particle was seen in the process of extrusion (arrow) after the fusion of the transport vesicle and the plasma membrane. The knoblike spikes surrounding the coronavirus were clearly visible. SARS-CoV spikes appeared short and stubby (16–17 nm) when compared to those of other coronaviruses (20 nm). This feature gave the virus a rosettelike appearance when viewed under the scanning electron microscope (arrowheads indicate extruded virus particles). The average size of the extracellular virus particles was 100–130 nm. The gold sputter coating can also increase in the diameters of the virus particles.

From 15 to 24 h after infection, the virus was exported prolifically at the pseudopodia and cell surfaces (Figure 3A–C, arrows). The surface imaging clearly showed the profuse presence of extracellular virus (arrows). High magnification scanning electron microscopy images of the SARS-CoV form and structure (Figure 3C, arrows)

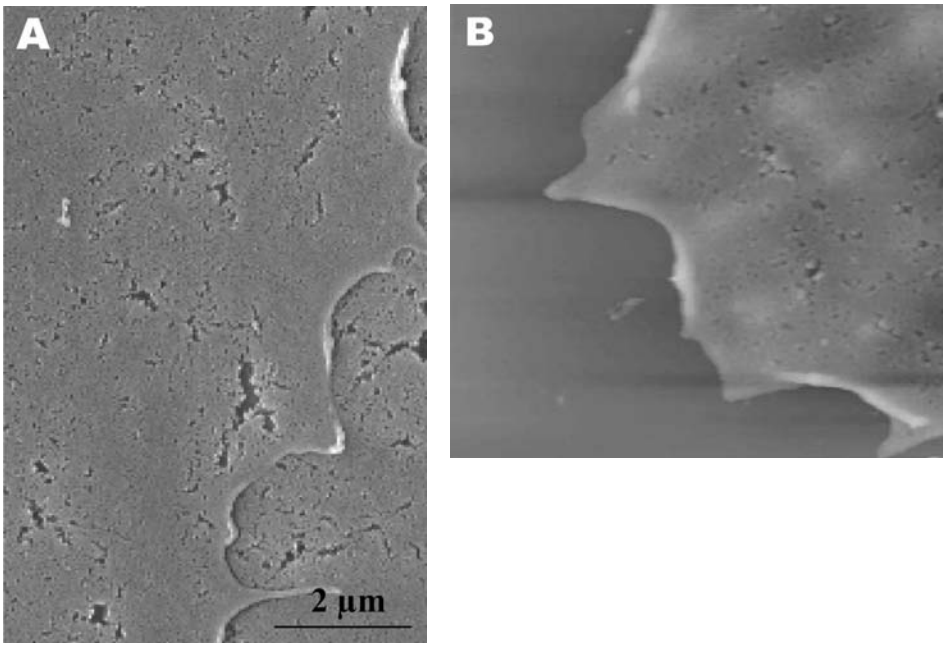

Figure 1. Scanning electron (A) and atomic force (B) microscopy images of uninfected Vero cells. A) Under the scanning electron microscope, uninfected cells look relatively flat with minimal surface morphology. No pronounced pseudopodia are visible on the cell edge or surfaces. B) Atomic force microscopy confirms the form and structure seen in panel A. Cell surface is uniformly flat.

appeared to correlate well with those images that used negative staining and TEM (Figure 3C, inset). The knoblike spikes were short and stubby in the negative staining image as well. Online Figure 3D (available at http://www.cdc.gov/ncidod/EID/vol10no11/04-0195-G3.htm) shows virus particles were also exported out from the surface of the pseudopodia (arrows).

A virus particle in the process of extrusion at the cell plasma membrane was captured with the atomic force microscope at 15 hours after infection. Although the proposed mechanism for export of the virus to the extracellular space is through fusion of the transport vesicle membrane at the cell surface, this process seemed to result in localized breaching at the plasma membrane, where the virus extrusion occurred (Figure 4A, thin arrows). Although fixed and gold-coated samples were used in this study, the atomic force microscope delivered high-resolution images. Unfortunately, the knoblike spikes for this virus were not well illustrated in Figure 4A. A three-dimensional reconstruction (Figure 4B) shows that the virus particle was extruding from a much-thickened cell periphery (arrow). The knoblike structures on the virus surface were further confirmed by atomic force microscopy (online Figure 4C, available at http://www.cdc.gov/ncidod/EID/vol10no11/04-0195-G4.htm).

The thickened edges of the infected cells were ruffled and appeared to comprise layers of folded membranes (Figure 5A and 5B and online Figure 5C, available at

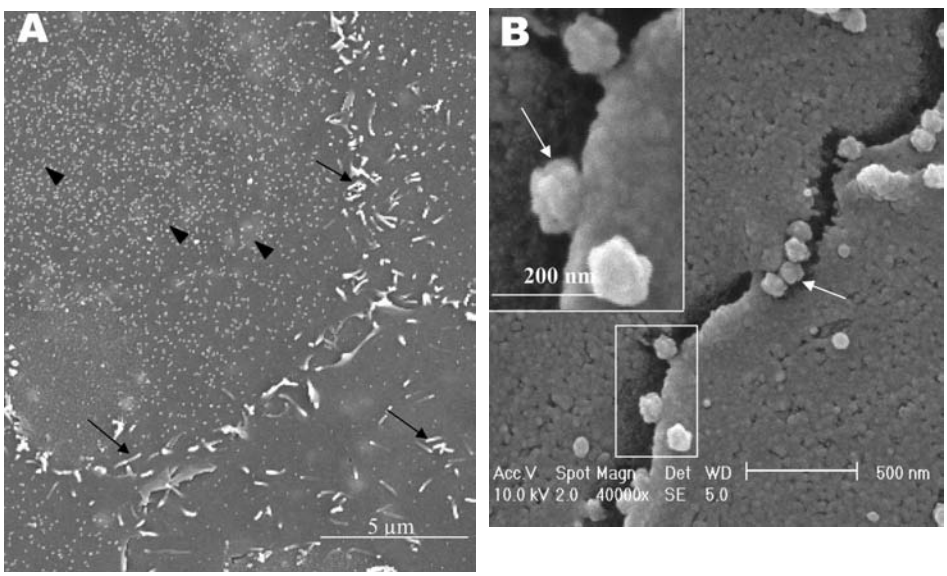

Figure 2. Scanning electron microscopy of Vero E6 cells infected with severe acute respiratory syndrome–associated coronavirus at 15 h after infection. A) One pronounced surface morphologic change is the proliferation of psuedopodia at the cell periphery (arrows). Some pseudopodia are also developing on the cell surface. Some cells appear to have large amount of extracellular virus on the cell surface (arrowhead), whereas neighboring cells seem deprived of any extracelluar virus particles. B) Virus particles are protruding from the edge of cells (arrows). Inset shows the boxed area at higher magnification. Virus particles appear knobby and rosettelike.

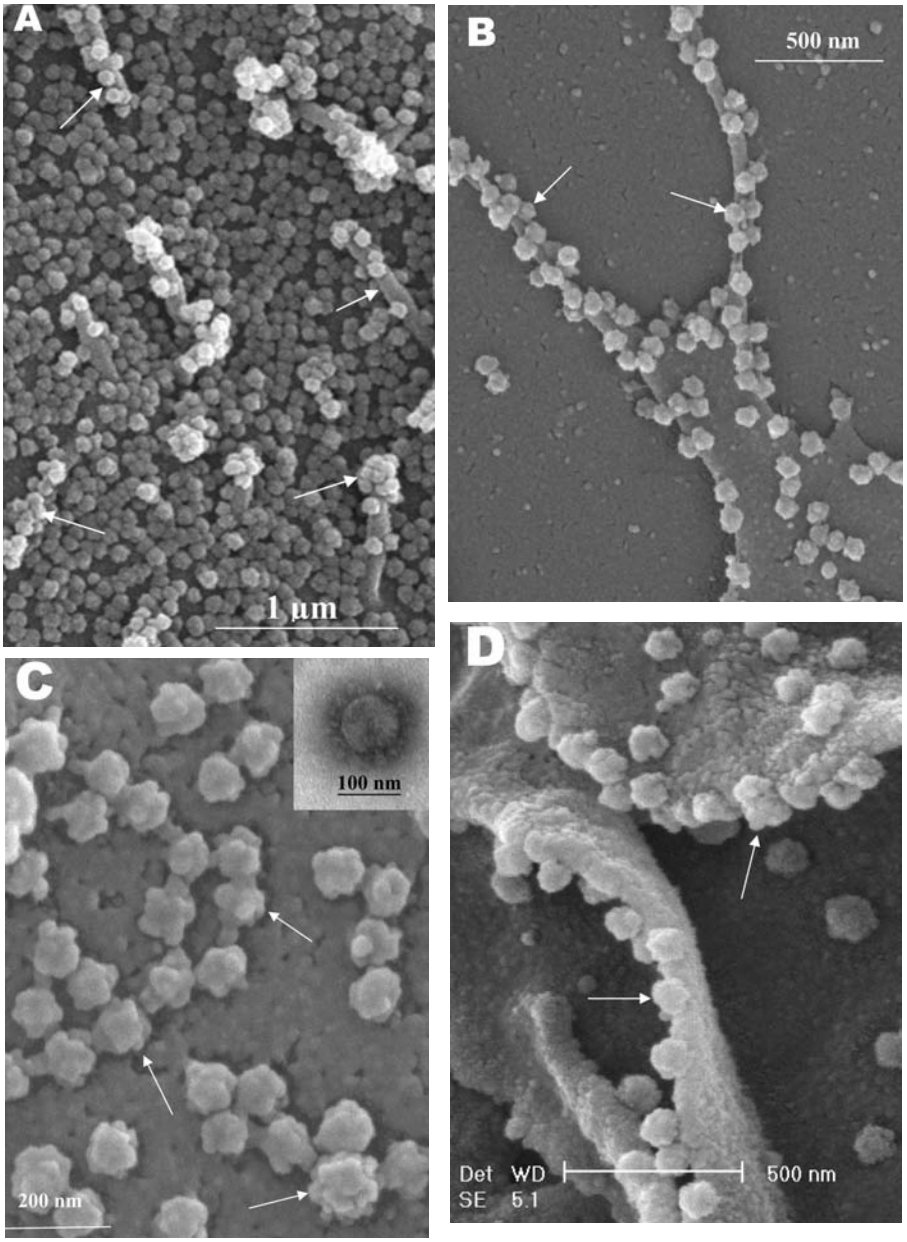

Figure 3. Scanning electron microscopy of Vero E6 cells infected with severe acute respiratory syndrome–associated coronavirus at 24 h after infection. A) Cell surface is covered with extracellular progeny virus particles, and progeny virus are being extruded from or attached to numerous pseudopodia on infected cell surface (arrows). B) A higher magnification micrograph of the virus-clustered pseudopodia (arrows). C) Rosettelike appearance of the matured virus particles (arrows). The scanning electron microscopy image complements the form and structure of the virus seen with negative staining (inset) under transmission electron microscopy. D) Arrows indicate virus particles being exported from the surfaces of the filopodia.

http://www.cdc.gov/ncidod/EID/vol10no11/04-0195-G5.htm). The layered/folded effects at the edge of cells were pronounced in the height image under the atomic force microscopy and scanning electron micrographs. The arrowheads show the virus particles.

Virus particles (arrowheads) could still be exported out of the puffy edge (Figure 6A, arrows). A three-dimensional reconstruction (Figure 6B) of the height image in Figure 6A shows puffy fronts of the cell edge (arrows) with many virus particles just underneath the surface awaiting extrusion. The large number of progeny virus particles at the cell edge may have resulted in this thickened appearance. Virus particles (arrowheads) were present on other parts of the cell surface as well. Thick white arrow shows a clump of virus particles just underneath the plasma membrane.

Closer examination of the virus-induced changes at the subcellular surfaces of the infected cells, by using the hard tapping mode under the atomic force microscope, showed the involvement of the cell cytoskeleton at late infection. In Figure 7A, gross thickening of the cell skeletal filaments was seen in the cytoplasm (arrowhead) and pseudopodia (arrows). At higher resolution, thickening of the filaments at the edge of cells was obvious (Figure 7B, arrows). These filaments, which ran parallel to the cell edge, could be the enhanced actin filaments, and together

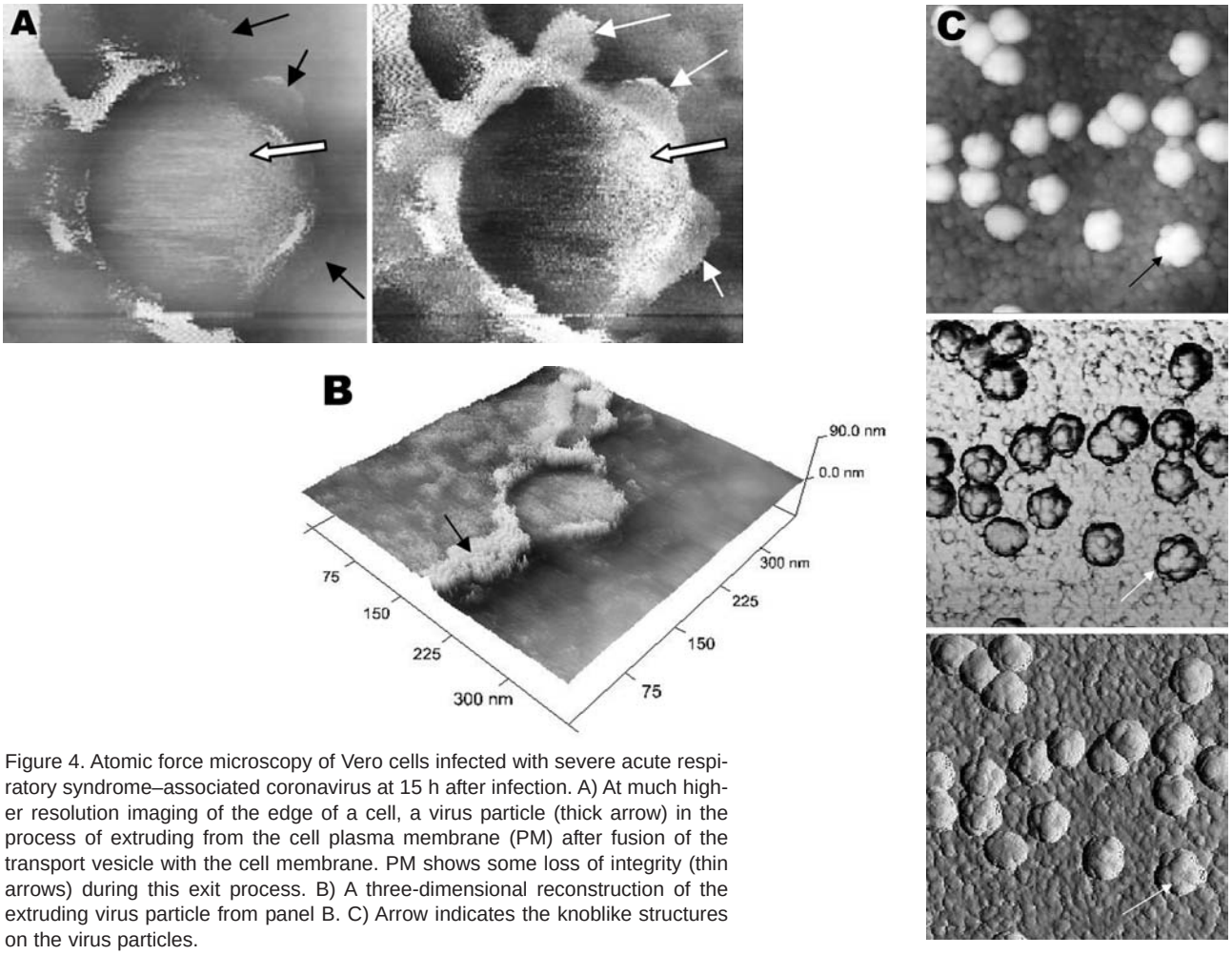

Figure 4. Atomic force microscopy of Vero cells infected with severe acute respiratory syndrome–associated coronavirus at 15 h after infection. A) At much higher resolution imaging of the edge of a cell, a virus particle (thick arrow) in the process of extruding from the cell plasma membrane (PM) after fusion of the transport vesicle with the cell membrane. PM shows some loss of integrity (thin arrows) during this exit process. B) A three-dimensional reconstruction of the extruding virus particle from panel B. C) Arrow indicates the knoblike structures on the virus particles.

with the accumulated progeny virus particles, could have caused the bulky, puffy-cell periphery.

Discussion

By using transmission electron microscopy, recent studies (10,11) showed the entry events and prolific growth of SARS-CoV in Vero E6 cells. SARS-CoV enters the cell by direct fusion and has a latent period of only 6 h. High numbers of progeny virus particles assemble in the swollen Golgi sacs before export to the external surface.

Transmission electron microscopy of ultrathin sections gave good intracellular information but was not able to give a gross morphologic landscape of the infected cells. Surface topographic changes induced by SARS-CoV at maturation and late stages of infections were the focus of this study. The virus-induced modifications at the cell surface or subcellular surface could relate to the eventual destruction of the infected cells as well as shed light on the extrusion mechanism of the progeny virus particles from the cell surface.

Scanning electron microscopy, an established technique, gives a three-dimensional overview of the virus and the infected cell surfaces. Another high-resolution device used in this study is the atomic force microscope. It is also gaining popularity in areas of life science research (23–29). Most of these studies were on purified macromolecules. However, the atomic force microscope has also become a virologic standard in recent years (30–33). A recent study on HIV and HIV-infected lymphocytes (34) demonstrated the strength of this technique for virology.

The application of these two selected techniques to study the late SARS virus–induced changes in Vero cells was rewarding. The SARS-CoV knobby/rosettelike structures were seen in a three-dimensional form under the scanning electron and atomic microscopy (Figures 2B, 4C-online). The spikes seemed shorter (16–17 nm) than those of other coronaviruses. At this stage, it is speculative if this could be due to the lack of the hemagglutinin-esterase protein (8,35) in the spike glycoprotein of this

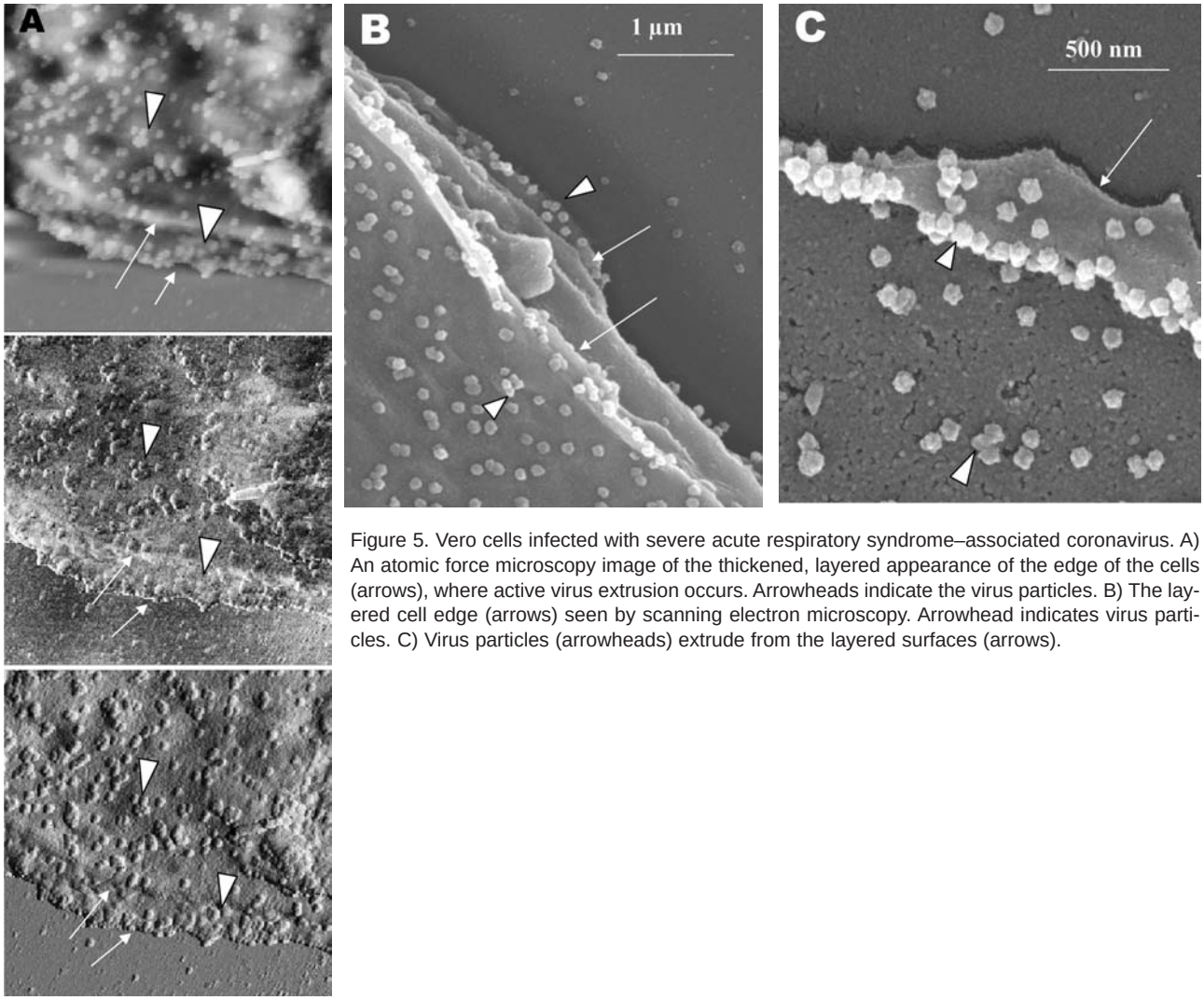

Figure 5. Vero cells infected with severe acute respiratory syndrome–associated coronavirus. A) An atomic force microscopy image of the thickened, layered appearance of the edge of the cells (arrows), where active virus extrusion occurs. Arrowheads indicate the virus particles. B) The layered cell edge (arrows) seen by scanning electron microscopy. Arrowhead indicates virus particles. C) Virus particles (arrowheads) extrude from the layered surfaces (arrows).

virus. Further structural and functional studies should be performed to investigate this aspect and its relation to virus virulence.

The scanning electron microscopy studies showed prolific SARS-CoV on infected cell surface 15 hours after infection. Unlike ultrathin sectioning in transmission electron microscopy, the scanning techniques allow cell and virus surfaces to be viewed without invasive manipulation. In addition to the large amount of extracellular virus particles on most cells, proliferation of the pseudopodia in the infected cells was pronounced (Figure 2A compared to Figure 1). These pseudopodia increase the surface area of the cells as active maturation sites of virus (Figures 3A and 3B).

Although the scanning electron microscope was able to show virus particles in the process of extruding (Figure 2B, Figure 3A and B) from the cells, the image derived with the atomic force microscope was superior in resolution. A virus particle was seen pushing out of the cell plasma membrane (Figure 4A), which resulted in localized loss of membrane integrity at the site. Since prolific extrusion of the progeny virus particles occurred at this late stage of infection, the frequent loss of plasma membrane integrity could compromise the physiologic status of the infected cells and lead to cell death.

Fifteen hours after infection, ruffled, puffy peripheries were visible in infected cells (Figures 4B, 5, and 6) and not seen in uninfected cells (Figure 1). This feature was not obvious under the transmission electron microscopy (11). Subcellular imaging of the thickened edge of the cells showed numerous progeny virus particles awaiting extrusion (Figure 6B, arrows). The actin filaments that were parallel to the cell edge appeared to have thickened (Figures 7A and B compared to Figures 1A and lB). The enhanced presence of the actin filaments could assist in providing the bending force to expel the progeny virus particles to the exterior. Bohn and colleagues (36) suggested that the forces resulting from the vectorial growth of the

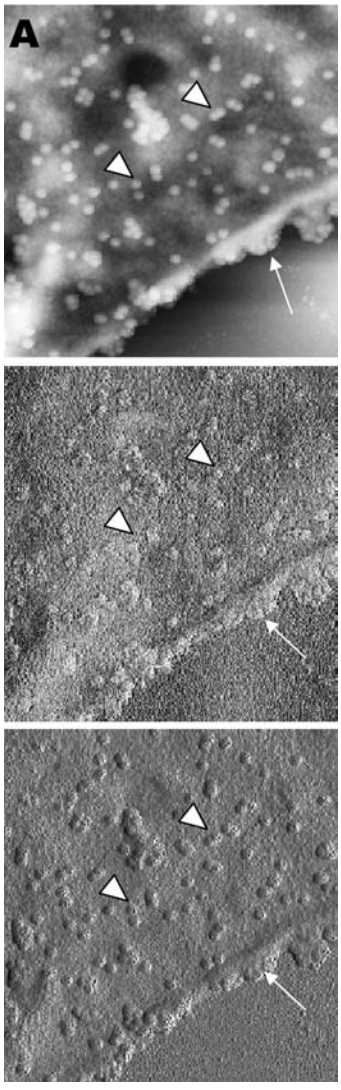

Figure 6. Atomic force microscopy of Vero cells infected with severe acute respiratory syndrome–associated coronavirus. A) High activity of virus extrusion at the thickened edge of the infected cells (arrow). Arrowheads indicate virus particles. B) A three-dimensional reconstruction of the image in panel A shows the puffy edge of infected cells. Many intracellular viruses are visible just under the plasma membrane (arrows). Extruded virus particles are present on other areas of the cell surface (arrowheads). Thick white arrow shows a large clump of virus particles just beneath the plasma membrane.

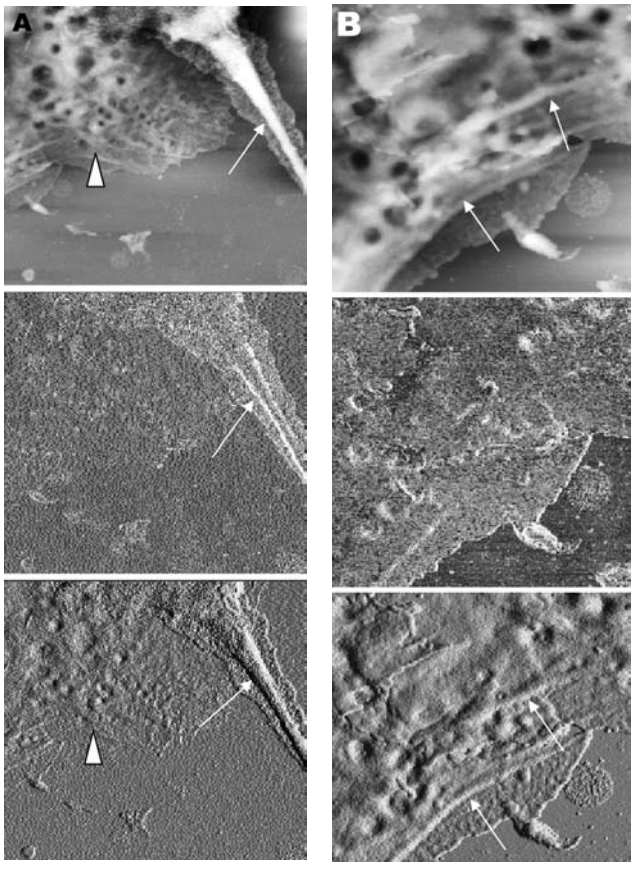

Figure 7. Vero cells infected with severe acute respiratory syndrome–associated coronavirus at 15 h after infection. A and B) When the hard tapping mode of the atomic force microscope is used, thickened cell cytoskeletal filaments are found below the subcellular surface of the cells. A) Enhanced cytoskeletal network of the cytoplasmic region (arrowhead). Arrow shows the much-thickened filaments within the pseudopodia of the cell. B) At high resolution, the arrows show the thickened cytoskeletal filaments along the cell periphery. The height and amplitude images clearly show the cytoskeletal filaments parallel to the cell edge.

actin filaments contributed to membrane bending at the site of virus maturation. Actin filaments have also been reported to be directly involved in the budding of both enveloped DNA and RNA viruses (37–40).

In summary, the cellular cytoskeleton network is involved in the SARS-CoV maturation and possibly replication process. The constant loss of membrane integrity attributable to the prolific progeny virus extrusion resulted in disintegration of infected cells.

Acknowledgments

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Evaluating Human Papillomavirus Vaccination Programs

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Human papillomavirus (HPV) has been implicated as the primary etiologic agent of cervical cancer. Potential vaccines against high-risk HPV types are in clinical trials. We evaluated vaccination programs with a vaccine against HPV-16 and HPV-18. We developed disease transmission models that estimated HPV prevalence and infection rates for the population overall, by age group, by level of sexual activity within each age group, and by sex. Data were based on clinical trials and published and unpublished sources. An HPV-16/18 vaccine for 12-year-old girls would reduce cohort cervical cancer cases by 61.8%, with a cost-effectiveness ratio of $14,583 per quality-adjusted life year (QALY). Including male participants in a vaccine rollout would further reduce cervical cancer cases by 2.2% at an incremental cost-effectiveness ratio of $442,039/QALY compared to female-only vaccination. Vaccination against HPV-16 and HPV-18 can be cost-effective, although including male participants in a vaccination program is generally not cost-effective, compared to female-only vaccination.

With 370,000 cases per year and a death rate of approximately 50%, cervical cancer is the third most common malignancy in women worldwide (1,2). Epidemiologic and laboratory evidence has implicated certain types of human papillomavirus (HPV) as the etiologic agents of cervical cancer (3,4). On the basis of this evidence, effort is under way to develop an HPV vaccine that targets these oncogenic HPV types (5).

Clinical trials of preliminary vaccines in humans began in the late 1990s (6). Recent data from an ongoing phase II trial (7) look very positive, demonstrating that an HPV-16 vaccine can prevent HPV infection and precancerous lesions in vaccinated women. These data provide hope that an HPV vaccine may be a reality within 5 to 10 years. Public health officials will then need to make important decisions regarding who and when to vaccinate and what level of vaccine penetration is necessary to substantially reduce disease prevalence.

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Central to this discussion is the question of whether both sexes should be vaccinated. The general assumption in the literature is that men and boys should be vaccinated (5,6,8,9). Although long-term sequelae of HPV infection for men is on average less serious (particularly for heterosexual men), men act as vectors for infection. Including men and boys in a vaccine program would enhance herd immunity and decrease overall incidence of cervical cancer. In this article, we evaluate the benefit and cost-effectiveness of adopting a vaccination strategy for both sexes, compared with that of adopting a female-only strategy. The incremental cost-effectiveness of a vaccination rollout strategy is calculated by dividing the difference in costs between strategies by the difference in quality-adjusted life expectancy.

Because results of the long-term phase III/IV trial are not available, the efficacy of the HPV vaccine is still unknown. Also, acceptance of an HPV vaccine is likely to vary substantially. Resistance to a vaccine may arise because HPV is a sexually transmitted disease (6,10), although recent studies suggest that an HPV vaccine may be reasonably well accepted (11). We therefore evaluated a wide range of vaccine efficacies and population penetrations to understand what is required for a female-only program to achieve sizeable benefit and to identify the scenarios in which incremental male vaccination makes most sense.

Methods

To capture the effect of a male vaccination program on female HPV infection rates and cervical cancer incidence, we needed to directly model the effect of vaccination on HPV disease transmission dynamics. Therefore, we developed disease-transmission models for HPV-16 and HPV-18, the types associated with most cervical cancer cases and the most likely to be included in HPV vaccines (3,6). For both types, the transmission models estimated HPV prevalence and infection rates for the U.S. population overall, by age group, level of sexual activity, and sex. The models also enabled us to evaluate the effect of

various vaccination programs on prevalence and infection rates.

Long-term equilibrium infection rates by age group, by level of sexual activity, and by sex for each vaccination scenario were determined in the transmission model. These infection rates were then incorporated into a probabilistic decision model. This model estimated the annual incidence of HPV-related precancerous lesions, lifetime cases of invasive cervical cancer, resulting cervical cancer deaths, and total cost of care for a given set of age-specific infection rates. By using the combination of the transmission and decision model, we estimated the effectiveness and cost-effectiveness of alternative vaccine rollout strategies.

Transmission Model Structure

We used Stella software (v7.0.3, High Performance Systems, Hanover, NH) to develop deterministic transmission models for heterosexual transmission of HPV types 16 and 18. Because level of sexual activity and HPV prevalence are highly age-dependent, we divided the population into nine age categories, from age 12 to age 50. We further divided each age category into four subcategories based on level of sexual activity (Table 1). HPV prevalence among their pool of sex partners, infectivity per infected partner, HPV shedding duration, and HPV infection rates were estimated for each age and activity group to develop a natural history transmission model. Vaccine penetration and efficacy were added to evaluate the effect of potential vaccine programs.

In our analysis, persons of both sexes were either HPV infected or uninfected at the beginning of each time period. In each period, uninfected persons could remain uninfected or become infected, on the basis of infection rates by age category (Figure 1). Infection rates were determined by number of sex partners, HPV prevalence among pool of sex partners, and infectivity per infected partner. HPV prevalence among the pool of sex partners was a function of HPV prevalence by age and risk group, and by sexual mixing patterns (preference of partners in different age groups for partners in different sexual classes) between age groups and between high- and low-risk sexual activity groups (Table 1). Details regarding the transmission model can be found in the online Appendix (http://www.cdc.gov/ncidod/EID/vol10no11/04-0222_app.htm).

Transmission Model Data

Sex Partnering

The level of sexual activity and mixing patterns between subgroups can affect the transmission dynamics of a sexually transmitted disease (23,24). Table 1 shows our estimates for these variables, based on a survey of the published literature. On average, the number of new sex partners per year for a person in our cohort increases from onset of sexual activity to age 24 and then decreases through age 50 (12–14). Mixing between sexual activity groups was assumed to be assortive, with a moderate preference to select partners in similar sexual activity groups (22). Mixing between age groups was predominantly older men with younger women (12–14).

Duration of HPV Shedding

Persons infected with HPV in a given period are assumed initially to be actively shedding virus and therefore contagious. In subsequent periods, infections can completely resolve or become dormant. Persons whose infections resolve before precancerous lesions develop are assumed to be at no risk for HPV-related cervical cancers, unless they become reinfected with the virus. Persons for

Table 1. Input variables[a,b]

Age category (y)	New sex partners/y (%) (12–14)								Mixing between age categories (%) (12–14)[c]						Initial HPV prevalence (%) (15–18)[d]				Duration HPV shedding (%) (19–21)[e]	
	Female				Male				Female			Male			HPV 16		HPV 18		Stop shedding	Completely regress
	0	1	2–4	5+	0	1	2–4	5+	<	=	>	<	=	>	Female	Male	Female	Male		
<18	64	30	5	1	57	30	11	1		64	36		90	10	2.6	3.5	0.9	1.2	55	49
18–20	55	26	15	4	50	25	19	6	1	61	38	18	72	11	4.3	5.0	1.8	2.1	55	49
21–23	55	26	15	4	50	25	19	6	3	59	38	32	58	10	4.6	5.0	2.2	2.3	55	49
24–26	76	19	4	1	66	21	12	2	11	51	38	34	56	10	3.0	3.4	1.5	1.7	37	33
27–29	83	12	4	1	71	15	12	2	11	51	38	34	56	10	1.7	2.7	0.8	1.4	37	33
30–34	89	7	4	1	76	10	12	2	10	49	41	38	49	13	1.0	2.1	0.5	1.1	37	7
35–39	90	6	3	0	81	9	9	1	13	50	37	36	49	15	0.7	1.5	0.4	0.8	37	7
40–44	90	6	3	0	81	9	9	1	15	48	37	39	47	15	0.5	1.1	0.3	0.6	37	7
≥45	94	5	1	0	90	6	3	0	15	85		39	62		0.4	0.7	0.2	0.4	37	7

[a]HPV, human papillomavirus.
[b]Mixing between sexual activity categories was assumed to be assortive (22). Relative preference for within-group mixing was estimated by [% of potential partners in group X] / [(% of potential partners in group X) + α(1 – % of potential partners in group X)], where α (the assortment variable) ranged from 0.4 for relatively assortive mixing (base-case value) to –0.4 for relatively disassortive mixing.
[c]For each age group, percentage of partners for persons who are in younger (<), the same (=), or older (>) age groups.
[d]Estimate of the prevaccination natural history of HPV infection.
[e]Probability that within 1 year a person of a given age group will stop shedding HPV and the probability that HPV infection will completely regress.

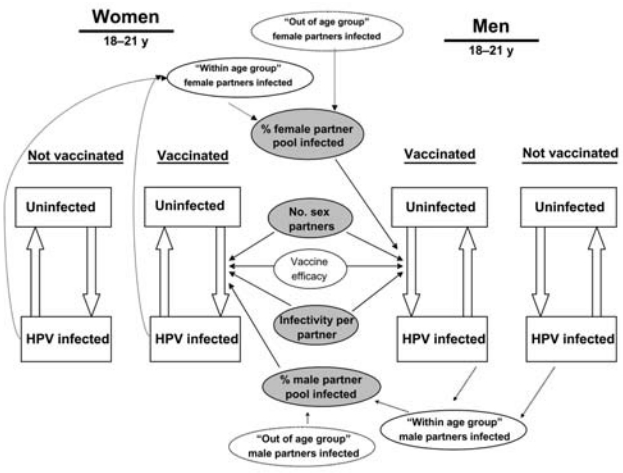

Figure 1. Schematic of the transmission model. The model is divided into nine age categories, with four subcategories per age group (not shown) based on different levels of sexual activity. In each period, uninfected persons can become infected. Infection rates are based on number of sexual partners per year, infectivity per infected partner, and percentage of potential partners who are infected. These variables are age- and risk-group specific. Infection rates for vaccinated persons also depend on the estimated vaccine efficacy. Percentage of potential partners infected includes partners within an age group and potential partners from younger and older age groups. Estimated mixing patterns between age groups differ by sex and age category.

whom the virus has gone into a dormant state can no longer transmit the virus, but they remain at increased risk for precancerous lesions and cancer in the future (Table 1).

Infectivity per Infected Partner

By using our estimates of HPV prevalence among pools of sex partners, numbers of new sex partners, sexual mixing patterns, and duration of HPV shedding, we derived estimates for infectivity per infected partner for persons of both sexes in each age group in the absence of a vaccination program. Infectivity was highest for women and men <18 years, at ≈0.35 infections per infected partner. This number dropped gradually for older age categories (to ≈0.15 infections per infected partner), representing increased resistance to infection and possible changes in sexual activity and practices in these age groups.

HPV Vaccine Characteristics

We assumed that the HPV vaccine would initially be administered by a series of three injections to 12-year-old girls. In our base-case analysis, booster shots would be required for persons in their early 20s. In this scenario, the protective effect of the vaccine lasts for 10 years after the most recent booster. We assumed that the vaccine had 90% efficacy against both HPV-16 and HPV-18 and was given to girls at age 12, with a booster at 22. We assumed 70% of girls were vaccinated, with a vaccine cost of $300 for the initial vaccination (three doses) and $100 for the booster.

Decision Model Structure and Assumptions

In a previous analysis (25), we modeled the overall progression of high-risk oncogenic HPV types to different stages of cervical dysplasia and cancer. In our current analysis, we adapted this model to evaluate the natural history and vaccination scenarios regarding HPV-16 and HPV-18. Estimates regarding Pap screening, lesion treatment, cancer progression and survival, costs, and utilities are based upon our previous analysis (25). Specific progression rate of HPV-16 and HPV-18 to different stages of cervical dysplasia and cancer were estimated from the literature (15,19,20,26,27).

Model Validation

To validate the model, we compared the incidence of cervical cancer cases and deaths predicted by the prevaccination natural history arm of our model with those reported in the Surveillance, Epidemiology, and End Results (SEER) registry (28). Our model's annual rates of cervical cancer cases and deaths matched 2001 SEER estimates within 10%. The predicted age-specific prevalence of HPV infection in our natural history arm also has a shape and peak of similar magnitude to that reported in the literature (15–18).

Results

Base-Case Analysis

Under our base-case scenario, vaccinated girls would experience a 61.8% overall reduction in acquiring cervical cancers over a lifetime. The analysis predicted, given the current U.S. population of 12-year-old girls (approximately 2.0 million), that the number of expected lifetime cases of cervical cancer related to HPV-16 or HPV-18 would drop from 9,147 to 422, a 95.4% reduction. This strategy would add an average of 6.1 quality-adjusted days of life per woman and have a cost-effectiveness ratio of $14,583 per quality-adjusted life-year (QALY) gained compared to the current environment (Table 2).

Vaccinating Men and Boys

If both sexes were vaccinated with an HPV-16/18 vaccine, total cervical cancer cases in that cohort would drop by 63.9%, compared to the number of cases in the scenario before vaccination. The number of cancer cases related to HPV-16 or HPV-18 would decrease from a prevaccination 9,147 to 113, a 98.8% drop from the number in the prevaccination scenario. Expanding the vaccination program to men and boys would add an incremental 0.21 quality-adjusted days of life per woman at a cost-effectiveness

Table 2. Total discounted healthcare costs, total discounted life expectancy in years, and total quality-adjusted discounted lifetime expectancy in years are presented for prevaccination, and for female-only and male + female vaccination scenarios.

Outcome	No vaccination	HPV-16/18 vaccination	
		Female-only[a]	Female + male[b]
Cost, $	40,423	40,667	40,929
Incremental cost, $		244	261
Life expectancy, y	28.7975	28.8112	28.8117
Incremental life expectancy, d		5.0	0.18
Quality-adjusted life expectancy, y	27.7422	27.7590	27.7596
Incremental quality-adjusted life expectancy, d		6.1	0.21
Incremental cost-effectiveness			
$ per life-year		17,802	534,317
$ per quality-adjusted life-year		14,583	442,039
% reduction in lifetime cervical cancer cases		61.8	2.2

[a]Incremental to no vaccination strategy.
[b]Incremental to a female-only vaccination strategy.

ratio of $442,039/QALY compared to the female-only strategy (Table 2).

Vaccine Penetration and Efficacy

Figure 2A shows how varying the vaccine coverage of a female-only HPV-16/18 vaccination program affects the number of lifetime cervical cancer cases. As expected, as vaccine coverage increases, the number of cervical cancer cases decreases. However, based on scenarios that used our transmission model, the relationship is not linear. Because of the benefits of herd immunity, vaccinating even a relatively small portion of the target population leads to substantial decreases in disease prevalence and resulting negative sequelae relative to prevaccination rates. Figure 2A also illustrates the effect of vaccinating both sexes. A combined male-female program always results in lower levels of cohort cervical cancer cases than a female-only program. However, this difference is only large when levels of female vaccine penetration are low.

Figure 2B shows the cost-effectiveness of HPV-16/18 vaccination programs compared to the current environment as coverage varies. The cost-effectiveness of female-only vaccination is attractive at all ranges of vaccine penetration. At lower vaccine penetration levels, including male participants in the vaccination program also becomes cost-effective. For example, at 30% female vaccine penetration, including male participants is reasonably cost-effective at $40,865/QALY compared to vaccinating female participants only. Figures 2C and 2D show similar data for changes in vaccine efficacy.

Vaccination Age

Our analysis assumes that vaccination would focus on children 12 years of age. We considered alternative vaccination strategies that would focus on either infants or persons 18 years of age. Because most women are not sexually active until after age 12, focusing on infants or 12-year-old children leads to approximately the same decrease in lifetime cases of cervical cancer. However, delaying initial vaccination until age 18 leads to only a 54.7% decrease in the number of cancer cases in this cohort. If focusing on the older age group also leads to a decrease in vaccine penetration (60%), then program effectiveness drops further to a 50.9% decrease in lifetime cervical cancer cases in this cohort.

We also considered how the optimal vaccination age was affected if the efficacy of the vaccine waned. If the vaccine efficacy waned over 10 years and no booster was provided, a vaccination program that targeted 18-year-old women would dominate one which targeted 12-year-old girls. In this scenario the cost-effectiveness of also vaccinating 18-year-old men would be economically favorable, with a cost-effectiveness of $57,795/QALY compared to the cost-effectiveness of vaccinating women only. If, however, two booster shots were given at 5-year intervals to maintain the vaccine's efficacy, 12-year-old girls would return to being the optimal vaccination group, but the cost-effectiveness of vaccinating boys would increase to $388,368/QALY.

Effect of Vaccination over Time and Catch-up Vaccination

Under our base-case scenario with an HPV-16/18 vaccine, the first cohort of vaccinated 12-year-old girls would experience a 29.7% decrease in overall cervical cancer cases at a cost-effectiveness of $27,566/QALY, compared to their experience without vaccination. Vaccinating boys would cost $285,776/QALY compared with a female-only program to reduce cervical cancer cases an additional 4.7%. In time, however, lifetime cervical cancer cases would reach a steady-state of ≈62% of prevaccination level. Thus, even the first cohort would experience almost half of the achievable benefit of a long-term vaccination program. Table 3 displays the average reduction in lifetime cervical cancer risk for girls vaccinated at age 12 through a large-scale vaccination program, compared to the

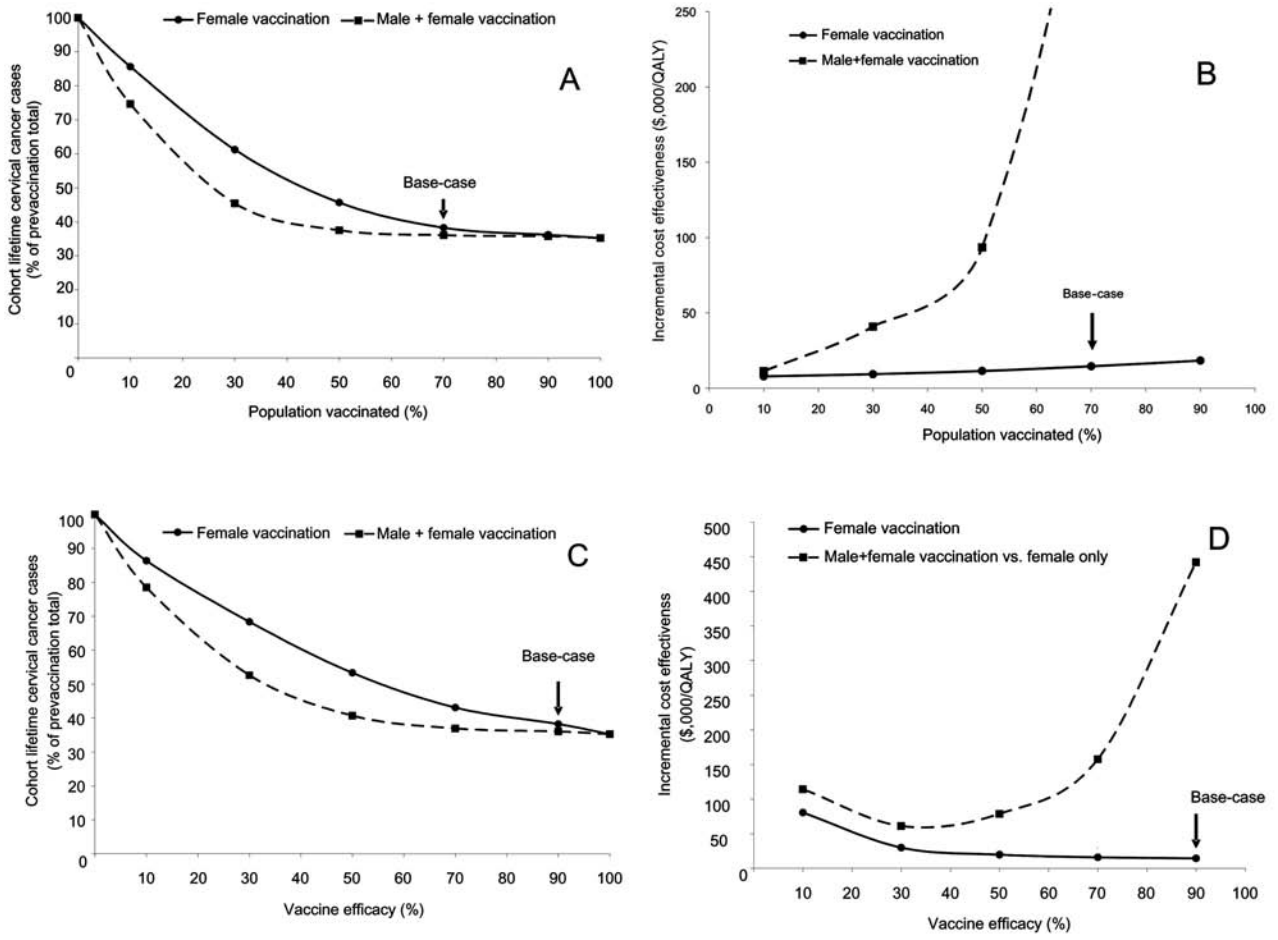

Figure 2. A) Vaccine penetration scenario. Relationship between percentage of the population receiving the vaccine and the number of lifetime cervical cancer cases. The solid line represents a female-only vaccination strategy. The dashed line represents a strategy of vaccinating both sexes. The arrow indicates the base-case scenario of a female-only strategy with 70% penetration. B) Vaccine penetration scenario. Relationship between percentage of the population receiving the vaccine and program cost-effectiveness. The solid line represents the cost-effectiveness ($/quality-adjusted life-year [QALY]) of a female-only vaccination program compared to current practice. The dashed line represents the incremental cost-effectiveness of including male participants in a vaccine program compared to a female-only strategy. The arrow indicates the base-case scenario of a female-only program with 70% penetration. C) Vaccine efficacy scenario. Relationship between vaccine efficacy and the number of cohort lifetime cervical cancer cases. The solid line represents a female-only vaccination strategy. The dashed line represents a strategy of vaccinating both sexes. The arrow indicates the base-case scenario of a female-only strategy assuming 90% vaccine efficacy. D) Vaccine efficacy scenario. Relationship between vaccine efficacy and program cost-effectiveness. The solid line represents the cost-effectiveness ($/QALY) of a female-only vaccination program compared to current practice. The dashed line represents the incremental cost-effectiveness of including male participants in a vaccine program compared to a female-only strategy. The arrow indicates the base-case scenario of a female-only program at 90% vaccine efficacy.

reduction in risk to women ages 24 and 30 who opt for catch-up vaccination once a vaccine becomes available.

Pap Screening Guidelines

Although an HPV-16/18 vaccine would not protect against all oncogenic HPV strains, we wanted to explore whether the vaccine could sufficiently reduce the prevalence of cervical cancer and precancerous lesions to allow for less frequent cervical cancer screening. Our base-case analysis assumes that 71% of women get Pap smears every 2 years (29). Figure 3 presents the cost-effectiveness of moving to more or less frequent screening intervals, in the presence of an established vaccine program.

Sensitivity Analyses

We performed sensitivity analyses on a range of model variables. The female-only vaccination program remained economically attractive under a wide range of variable assumptions. However, the incremental benefit of vaccinating men and boys was sensitive to changes in key variables. Figure 4 shows one-way sensitivity analyses of the cost-effectiveness of incrementally vaccinating male

Table 3. Reduction in lifetime risk of cervical cancer

Cohort	% reduction in lifetime risk of cervical cancer
Full potential of program in 12-year-old girls	64
First cohort of 12-year-old girls vaccinated[a]	46
24-year-old women who receive catch-up vaccination[b]	35
30-year-old women who receive catch-up vaccination[b]	17

[a]This group experiences a lower reduction in cancer cases because many of their sex partners will be drawn from a population pool that has not been vaccinated.
[b]24- or 30-year-old women who opt for catch-up vaccination in the first year that the vaccine becomes available.

participants compared to the cost-effectiveness of female-only vaccination.

Discussion

By using a disease transmission model for the sexual transmission of HPV, we demonstrated that an HPV-16/18 vaccine would be cost-effective and could reduce lifetime cervical cancer cases by 61.8%. Although a universal vaccination program would have the greatest benefit, because of the benefits of herd immunity, a program that achieves even 70% coverage would dramatically reduce cohort lifetime cervical cancer cases.

Although the literature often suggests that men and boys should be included in an HPV vaccination program (5,6,8,9), our results suggest that this strategy may not be the most cost-effective public health strategy. Under our base-case assumptions, including men and boys in a vaccination program would further reduce infections and cancer cases only slightly, with an unattractive cost-effectiveness ratio of $442,039/QALY saved. In addition, the absolute cost of expanding coverage to men and boys is high. Assuming a $300 vaccine, achieving 50%–70% coverage for the current U.S. population of approximately 2.1 million 12-year-old boys would cost >$300 million annually.

In certain scenarios, such as those in which vaccine efficacy wanes rapidly without boosters or overall vaccine coverage is low, vaccinating male participants can have a substantial effect (Figure 4). In a recent article that modeled risk groups but not age groups, Hughes et al. (30) found that for a single-type HPV vaccine with a 10-year mean duration and no booster that was meant for 16-year-olds, a program focusing on girls would have only two thirds of the impact on HPV infection rates as a program focusing on both sexes. Modeling both risk and age groups, we found that the incremental cost-effectiveness ratio of vaccinating boys dropped to $51,646/QALY for a vaccine with rapidly waning efficacy and no booster. Also, if vaccination rates are lower among the most sexually active girls, the female-only vaccination strategy will be less effective. In sensitivity analyses, we demonstrated that vaccinating boys in such a situation would be reasonably cost-effective. For example, if vaccine penetration amongst the highest risk girls reached only 30%, the cost-effectiveness ratio of vaccinating boys drops from $442,039/QALY to $116,413/QALY. Nonetheless, even in this scenario, vaccinating boys is less cost-effective than achieving higher vaccine penetration in girls at high risk (analysis not shown).

We demonstrated that vaccinating women at the onset of sexual activity is cost-effective and will lead to the greatest reduction in cervical cancer incidence. Because we assume that the vaccine will require a booster after 10 years, focusing on 12-year-olds would be more cost-effective than focusing on infants ($27,600/QALY). If a vaccination program focusing on infants were more widely accepted, with initial coverage of 80% versus 70% in the base-case scenario, we would expect only an additional 1.2% decrease in overall lifetime incidence of cervical cancer, and the cost-effectiveness ratio would increase to $28,181/QALY. Focusing on 18-year-olds would limit the efficacy of the vaccine program and is not recommended unless focusing on younger groups is not possible.

We explored the effect of changing cervical cancer screening interval guidelines once a vaccine program was established (Figure 3). Even in a prevaccination environment, researchers found that moving from screening every 2 years to every year is not particularly cost-effective (31). Kulasingam and Myers recently found that Pap testing may be delayed to a later age than currently recommended when an HPV vaccine has been given; although that analysis did not include disease-transmission dynamics and

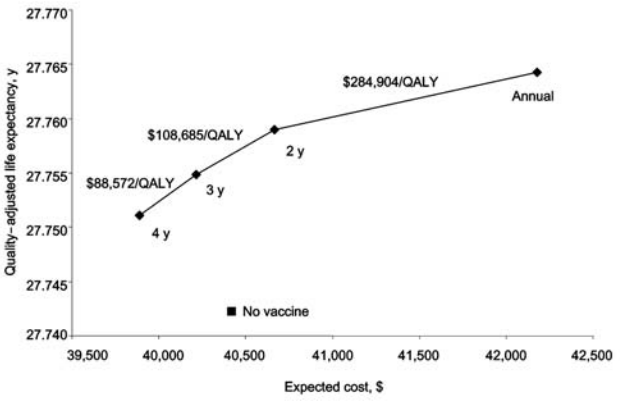

Figure 3. Effect of changing frequency with which vaccinated women receive a Pap test. The diamonds represent Pap testing annually, every 2 years (base case), every 3 years, and every 4 years. The x-axis represents the lifetime expected cost of the vaccination strategy; the y-axis is the quality-adjusted life expectancy in years. The incremental cost-effectiveness of increasing the frequency of Pap testing for vaccinated women is indicated numerically above the cost-effectiveness frontier. QALY, quality-adjusted life-year.

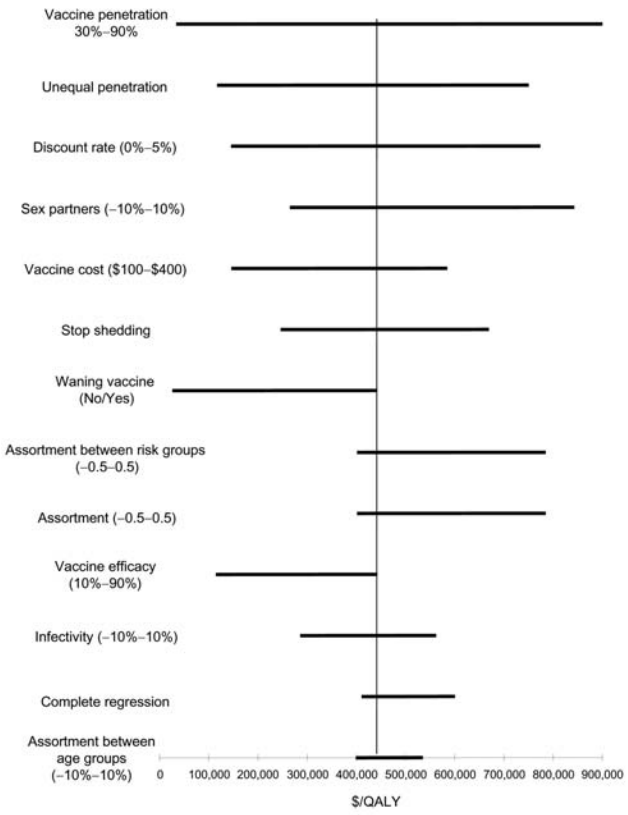

Figure 4. Tornado diagram representing the incremental cost-effectiveness ratios of one-way sensitivity analysis on vaccinating men and women compared to vaccinating women only. The vertical line represents the incremental cost-effectiveness ratio under base-case conditions. The sensitivity analysis range is displayed in parentheses next to each variable. Unequal penetration represents potential for lower (or higher) vaccine penetration in the highest risk groups, from 30% to 80% of target group, compared to 70% penetration in base case. QALY, quality-adjusted life-year.

predicted that broad-based immunization would decrease cervical cancer incidence by 17% (32). By using a disease-transmission model that predicts greater vaccine impact, we demonstrated that Pap testing vaccinated women every 3 or 4 years had a more powerful effect than a no-vaccine strategy (i.e., cost less and increased quality-adjusted life expectancy). With a vaccine program in place, moving from screening every 3 years to every 2 years cost >$100,000/QALY, while annual screening is not economically favorable (Figure 3). Given these data, with a vaccine program in place, physicians may be comfortable moving to less frequent screening.

We did not include in our analysis the effect of an HPV vaccine on several other cancers associated with HPV. We also did not examine the effect of vaccines targeting the nononcogenic HPV types most commonly associated with genital warts. Including the former would make the vaccine strategies appear to be even more cost-effective. The latter can be considered as a separate analysis, since a vaccine would offer little cross-protection between HPV types (5). Also, although some have suggested that lesion treatment protects against sequelae of future HPV infections (e.g., squamous intraepithelial lesions and cervical cancer) (30), we are not aware of evidence that supports this hypothesis, so we did not include it in our analysis. Including this potential benefit would diminish the cost-effectiveness of a future vaccine. Finally, our analysis does not examine targeted vaccination in men who are at high risk, for instance, in the community of men who have sex with men, in which HPV infection rates are higher than for the general population.

Although this analysis modeled vaccine programs in the United States, our results may have relevance for decision makers in less developed countries where public health resources are limited and cervical cancer death rates can be markedly higher than in the United States. These countries may have difficulty achieving high levels of vaccine penetration. However, because even modest vaccine coverage appears to substantially reduce cervical cancer cases, a partial vaccination program that includes specific populations might be more efficacious and cost-effective for these countries than alternative options, such as Pap or HPV screening.

Our analysis indicates that vaccinating 12-year-old girls with an HPV-16/18 vaccine would cost $14,583 /QALY, whereas vaccinating boys costs $442,039/QALY. In comparison, screening strategies of women for cervical cancer with Pap smears has been estimated to cost between $7,777 per life-year (LY) (quadrennial screening) and $166,000/LY (annual screening) and depends on the type of testing and prevalence of disease (31). Similarly, studies of hepatitis B vaccines have estimated costs from $4,800 to $16,000/QALY to selectively vaccinate at-risk populations versus universal infant vaccination or versus no vaccination, respectively (33).

Vaccine evaluations that do not include disease transmission can underestimate actual vaccine benefit (34–36). By modeling disease transmission by age category and risk grouping, we were able to estimate the effect of herd immunity, which we know from actual vaccine rollouts can be substantial (37,38). Prior cost-effectiveness analyses of potential HPV vaccines by our group (25) and others (32,39) have not included transmission by age category, multiple sexual activity subgroups, or the protective benefit of herd immunity. As a result, these analyses have likely underestimated the benefits of vaccination. In addition, previous approaches did not attempt to evaluate the cost-effectiveness of male vaccination. By modeling transmission by different age and risk groups, we also were able to address the issue of unequal vaccine penetration in high-risk groups, an important real world phenomenon.

Because an HPV vaccine is likely to be available in the future, public health officials will need to decide on HPV vaccine rollout strategies. Our analysis shows that a vaccine that protects against HPV-16/18 could be cost-effective and has the potential to substantially reduce cervical cancer rates. Additionally, under most scenarios, we showed that including men and boys in a vaccination program has a limited effect, which suggests that scarce healthcare resources could be used in a more productive manner. As ongoing clinical trials and vaccine development progress, we believe our analysis will provide public health officials with the tools needed to make optimal recommendations with limited resources.

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Mr. Taira is a fourth-year medical student at Stanford University and is affiliated with the Stanford Center for Primary Care and Outcomes Research. His research focuses on cost-effectiveness analyses and disease transmission dynamics within populations.

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Enhanced Identification of Postoperative Infections among Inpatients

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We evaluated antimicrobial exposure, discharge diagnoses, or both to identify surgical site infections (SSI). This retrospective cohort study in 13 hospitals involved weighted, random samples of records from 8,739 coronary artery bypass graft (CABG) procedures, 7,399 cesarean deliveries, and 6,175 breast procedures. We compared routine surveillance to detection through inpatient antimicrobial exposure (≥9 days for CABG, ≥2 days for cesareans, and ≥6 days for breast procedures), discharge diagnoses, or both. Together, all methods identified SSI after 7.4% of CABG, 5.0% of cesareans, and 2.0% of breast procedures. Antimicrobial exposure had the highest sensitivity, 88%–91%, compared with routine surveillance, 38%–64%. Diagnosis codes improved sensitivity of detection of antimicrobial exposure after cesareans. Record review confirmed SSI after 31% to 38% of procedures that met antimicrobial surveillance criteria. Sufficient antimicrobial exposure days, together with diagnosis codes for cesareans, identified more postoperative SSI than routine surveillance methods. This screening method was efficient, readily standardized, and suitable for most hospitals.

Preventing healthcare-associated infections, including surgical site infections (SSI), is an integral part of the national patient safety agenda developed in response to the Institute of Medicine's report, To Err is Human: Building a Safer Health System (1). Although nearly all hospitals monitor their SSI rates, no generally accepted active surveillance method is both reproducible and widely used. Fewer than 10% of hospitals participate in the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infection Surveillance System (NNIS). Many hospitals use surveillance systems based more or less closely on NNIS; most of these systems are labor-intensive and their sensitivity is typically unknown.

We therefore studied the ability of exposure to antimicrobial drugs and coded discharge diagnoses to identify SSI after three common procedures: coronary artery bypass graft (CABG) procedures, cesarean delivery, and breast procedures. We chose these measures because prior work suggested their usefulness (2,3), nearly all hospitals collect this information as part of routine patient care, and many hospitals store this information electronically.

Methods

We conducted this study in two phases in 13 hospitals affiliated with the seven CDC epicenters. Phase 1 involved seven teaching and community hospitals in eastern Massachusetts. Phase 2 involved hospitals in seven states. The study design was similar for each of the procedures, although the antimicrobial intervals required to trigger record review were procedure-specific and based on earlier work (2,3). We describe the methods in detail for CABG procedures and then provide additional information for cesarean delivery and breast procedures. The number of hospitals assessing the three procedures differed because of different practice patterns.

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CABG Procedures

Phase 1–Eastern Massachusetts Epicenter

We studied consecutive CABG procedures performed from April 1, 1998, through January 31, 1999, in four hospitals. Qualifying International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) procedure codes are listed in the online Appendix (http://www.cdc.gov/ncidod/eid/vol10no11/04-0572_app.htm). Infection control professionals performed prospective inpatient SSI surveillance, typically once or twice per week, using the NNIS definitions (4). The surgical sites usually were not observed directly by the infection control professionals. We included SSI detected during the initial hospital admission for the CABG procedure or any readmission to the same hospital that occurred within 60 days of the operative procedure. Weeks or months later, the hospitals' information systems and medical records were used to obtain information about antimicrobial drug exposure and discharge diagnoses.

Discharge Diagnosis Codes Screening and Antimicrobial Exposure Screening

We identified patients with ICD-9-CM discharge diagnosis codes that suggest SSI (see online Appendix at http://www.cdc.gov/ncidod/eid/vol10no11/04-0572_app.htm) from their initial hospitalization or readmission to the same hospital within 60 days of the operative procedure.

We identified patients for whom ≥9 days elapsed from the first to the last postoperative dates on which they received parenteral or oral antimicrobial drugs (i.e., an antimicrobial interval of ≥9 days), based on the results of prior work (2). The first postoperative day was ignored because antimicrobial prophylaxis was typically given at that time. Patients did not need to receive antimicrobial agents on each day or the same agent throughout the interval. For instance, a patient could meet the 9-day criterion by receiving cefazolin on the second postoperative day, no antimicrobial drug on postoperative days 3 through 10, then receive an oral quinolone on postoperative day 11. This definition simplified data collection and is nearly as efficient as a measure that required the same antimicrobial drug to be administered continuously during the interval (2). We also identified patients who received any oral or parenteral antimicrobial drug during a readmission to the same hospital within 60 days of the operative procedure. Antiviral drugs and antifungal agents were excluded.

Identification through Antimicrobial Exposure or ICD-9-CM Code and Interreviewer Reliability

Infection control professionals reviewed the medical records of all patients who met either the antimicrobial drug exposure or ICD-9-CM diagnosis code criteria but who had not been classified as infected during prospective NNIS-based surveillance. The infection control professionals used NNIS criteria to classify the patients' infection status. An NNIS-trained infection control professional who was not affiliated with any of the participating hospitals also reviewed the medical records of all patients who were classified as not having an SSI by routine surveillance but who met diagnosis code, antimicrobial drug exposure screening criteria, or both.

Analysis and Statistical Methods

Incidence rates of SSI, the sensitivity and the positive predictive value of original prospective surveillance, antimicrobial drug exposure screening, diagnosis code–screening, and combinations of these were determined against the standard criterion created by combining the SSI detected prospectively during routine surveillance and the SSI identified retrospectively when medical records were reassessed. We defined the positive predictive value of routine prospective surveillance to be 100%. Logistic regression was used to evaluate whether diagnosis codes and antimicrobial drug exposure were performed homogenously across the participating hospitals. The κ statistic was used to assess agreement in SSI classification between hospital-based infection control professionals and the external reviewer (SAS software, v. 8, SAS Institute, Cary, NC)

Phase 2–All Epicenters

One hospital participated from each of the six epicenters that performed CABG procedures. One hospital had also participated in phase 1. The study population included consecutive CABG procedures performed from July 1, 1999, through June 30, 2001, in the six hospitals.

The methods described for phase 1 were also used for phase 2, except that research personnel retrospectively reviewed the medical records of all patients who had been classified by routine surveillance as having SSI. In addition, research personnel also reviewed the medical records of a random sample of 200 patients who underwent CABG procedures at each hospital to identify patients with ICD-9-CM diagnosis codes suggestive of SSI, to extract antimicrobial drug exposure data, and to retrospectively reassess each patient for the presence of an SSI.

The total number of SSI was estimated by multiplying the SSI rate identified by medical record review in the random sample of patients not known to have SSI based on routine surveillance by the number of patients in the entire group who were not known to have SSI. This estimate was added to the number of SSI identified through routine surveillance to estimate an adjusted SSI rate for each hospital. The sensitivity and positive predictive value of original prospective surveillance, screening by antimicrobial drug

intervals, screening by diagnosis codes, and combinations of these were estimated by using the known sampling fractions to extrapolate to the source population. Binomial confidence intervals (CI) were calculated for SSI rates on the basis of the random sample and extrapolated to the source population (Stata software, v. 8.2, Stata Corporation, College Station, TX). Logistic regression was used to evaluate whether screening for SSI by diagnosis code and antimicrobial drug exposure was performed homogenously across the participating hospitals (SAS software, version 8, SAS Institute, Cary, NC).

Cesarean Deliveries

Phase 1–Eastern Massachusetts Epicenter

We studied consecutive cesarean deliveries performed from April 1, 1998, through January 31, 1999, in five hospitals. Qualifying procedure codes are listed in the online Appendix (http://www.cdc.gov/ncidod/eid/vol10no11/04-0572_app.htm). Each participating hospital performed routine inpatient SSI surveillance. We identified patients assigned an ICD-9-CM diagnosis code that suggested SSI (online Appendix), who met antimicrobial drug exposure criteria during the initial hospital admission or any readmission to the same hospital within 60 days of the operative procedure, or both. We used an antimicrobial drug interval of ≥2 days for cesarean deliveries. Medical record review and analysis were performed as described.

Phase 2–All Epicenters

One hospital from each of four epicenters evaluated cesarean deliveries occurring from July 1, 1999, through June 30, 2001. Two hospitals used the methods described. In two other hospitals that had not performed routine prospective inpatient surveillance for SSI, research personnel retrospectively reviewed the medical records of all patients who met either ICD-9-CM diagnosis code or antimicrobial exposure criteria, plus records from a random sample of 200 other patients.

The total number of SSI was estimated as described. For the hospitals without routine surveillance, the total number of SSI was estimated by multiplying the SSI rate in the random sample by the number of patients in the entire group who did not meet diagnosis code or antimicrobial exposure criteria. This estimate was added to the number of SSI identified through medical record review of patients who met diagnosis code or antimicrobial drug exposure criteria to calculate an estimated adjusted SSI rate for each hospital.

Breast Procedures

Phase 1–Eastern Massachusetts Epicenter

We studied consecutive breast procedures performed from April 1, 1998, through January 31, 1999, in seven hospitals (see procedure codes in the online Appendix). Routine inpatient SSI surveillance, ICD-9-CM diagnosis code (online Appendix) and antimicrobial drug exposure screening, and medical record review were performed as described. We used an antimicrobial interval of ≥6 days for breast procedures.

Phase 2–All Epicenters

One hospital from each of five Epicenters participated. Three of the five hospitals did not perform routine prospective inpatient surveillance for SSI after breast procedures. Methods for screening, sampling, estimating SSI rates, sensitivities, and positive predictive value were as described for cesarean deliveries.

Results

A total of 8,739 CABG procedures, 7,399 caesarean deliveries, and 6,175 breast procedures were assessed (Table 1). In addition to routine prospective surveillance as described, 189–451 charts per procedure type were reviewed at each hospital. Hospital-specific results are shown in the online Appendix (http://www.cdc.gov/ncidod/eid/vol10no11/04-0572_app.htm).

CABG Procedures

Phase 1

The overall SSI rate based on confirmed infections detected by any of the three methods was 6.3% (Table 2).

Table 1. Number of procedures and hospitals included in phase 1 (eastern Massachusetts epicenter) and phase 2 (all epicenters)

Procedures and phase	No. of procedures	No. of hospitals	Procedures per hospital (range)
Coronary artery bypass graft			
Phase 1	2,267	4	173–775
Phase 2	6,472	6	217–2,221
Cesarean delivery			
Phase 1	2,659	5	118–1,248
Phase 2	4,740	4	628–2,437
Breast procedures			
Phase 1	1,477	7	52–503
Phase 2	4,698	5	329–1,822

Table 2. SSI rates after CABG procedures, cesarean delivery, and breast procedures[a,b]

Procedure/phase	SSI rates detected by	
	% routine surveillance (SSI/ procedures) [95% CI]	Any method %[c] (SSI/procedures) [95% CI]
CABG		
Phase 1	4.9 (112/2,267) [4.1%–5.9%]	6.3 (142/2,267) [5.3%–7.3%]
Phase 2	4.6 (298/6,472) [4.1%–5.1%]	7.7 (501/6,472) [7.1%–8.9%]
Combined	4.7 (410/8,739)	7.4 (643/8,739)
Cesarean delivery		
Phase 1	1.6 (43/2,659) [1.2%–2.2%]	4.1 (110/2,659) [3.4%–5.0%]
Phase 2	1.6 (49/3,065)[d] [1.2%–2.1%]	5.5 (263/4,740) [4.8%–6.3%]
Combined	1.6 (92/5,724)	5.0 (373/7,399)
Breast procedures		
Phase 1	0.7 (10/1,477) [0.3%–1.2%]	0.9 (14/1,477) [0.5%–1.6%]
Phase 2	0.4 (7/1,765)[d] [0.2%–0.8%]	2.3 (110/4,698) [2.1%–2.8%]
Combined	0.5 (17/3,242)	2.0 (124/6,175)

[a]Based on routine surveillance and routine surveillance plus screening for antimicrobial drug exposure, discharge diagnosis codes, or both.
[b]SSI, surgical site infection; CABG, coronary artery bypass graft; CI, confidence interval.
[c]Routine, antimicrobial exposure, diagnosis codes.
[d]The total number of procedures is noted for the hospitals that had performed routine surveillance.

The sensitivities of routine prospective surveillance (79%) and antimicrobial drug exposure screening (80%) were essentially equal and both substantially exceeded that of ICD-9-CM diagnoses codes (61%) (Table 3). The positive predictive value of antimicrobial drug exposure (33%) was considerably lower than that for surveillance based on diagnosis codes (86%), which reflected the fact that 15% of patients met the antimicrobial drug exposure criteria compared with 4.5% of those who were assigned the screening diagnosis codes. The patients who met either the antimicrobial drug exposure or diagnosis code–screening criteria overlapped substantially, which resulted in the joint measure's having performance characteristics similar to that of antimicrobial drug exposure screening alone.

The SSI classification assigned by hospital-based and external reviewers agreed for 107 (82%) of 130 procedures, with an overall κ coefficient of 0.66 (95% CI 0.53, 0.79). κ coefficients did not vary significantly across hospitals (p = 0.11).

Phase 2

The overall rate of confirmed SSI based on the combination of methods was 7.7% (Table 2); approximately one third of these were deep sternal SSI (SSI rates of 2.2% for deep sternal, 2.5% for superficial sternal, 3.1% for superficial donor site, and 0.2% for deep donor site SSI). In contrast to phase 1, antimicrobial drug exposure screening (≥9 days) identified substantially more infections (sensitivity 91%) than routine surveillance (59%), which performed slightly better than coded discharge diagnoses (54%) (Table 3). The sensitivity did not vary meaningfully for different SSI types. The combination of a ≥9-day antimicrobial interval and discharge diagnoses identified 93% of SSI. The overall positive predictive values of antimicrobial drug screening, diagnosis code screening, and the combination of both were similar to those observed in phase 1, with higher values for diagnosis codes. The proportions of patients meeting the three screening criteria were also similar to the values observed in phase 1

Table 3. Sensitivity and positive predictive value of routine surveillance and screening by antimicrobial drug exposure, diagnosis codes, or both for identifying SSI after CABG procedures, cesarean delivery, and breast procedures[a]

Procedure/phase	Sensitivity[b] (%)				Positive predictive value[b] (%)		
	Routine surveillance	Antimicrobial exposure	Diagnosis code	Antimicrobial exposure and/or diagnosis code	Antimicrobial exposure	Diagnosis code	Antimicrobial exposure and/or diagnosis code
CABG							
Phase 1	79	80	61	87	33	86	35
Phase 2	59	91	54	93	36	84	36
Cesarean delivery							
Phase 1	39	90	48	96	42	61	42
Phase 2	38	84	78	97	37	67	38
Breast procedures							
Phase 1	71	71	50	79	19	58	20
Phase 2	33	94	70	96	33	79	33

[a]SSI, surgical site infections; CABG, coronary artery bypass graft.
[b]Compared to standard criteria comprised of all infections identified during prospective surveillance or medical record review.

Table 4. Percentage of patients who met the antimicrobial drug, diagnosis code–screening criteria, or both, after CABG procedures, cesarean delivery, and breast procedures[a]

Procedure and phase	% of patients meeting		
	Antimicrobial exposure criteria	Diagnosis code criteria	Antimicrobial exposure or diagnosis code criteria
CABG			
Phase 1	15.2	4.5	15.8
Phase 2	19.1	4.6	19.6
Cesarean delivery			
Phase 1	8.8	3.2	9.5
Phase 2	12.7	6.4	14.1
Breast procedures			
Phase 1	3.5	0.8	3.7
Phase 2	6.7	2.0	6.8

[a]CABG, coronary artery bypass graft.

(Table 4). A more liberal antimicrobial interval of ≥7 days negligibly increased sensitivity from 91% to 93%, reduced the positive predictive value to 30%, and increased the proportion of patients who met the criteria to 23% (online Appendix Table 4 available at http://www.cdc.gov/ncidod/eid/ vol10no11/ 04-0572_app.htm). We observed no significant heterogeneity in the performance of screening by antimicrobial threshold to detect SSI among the six hospitals (p = 0.9).

Cesarean Delivery Surveillance

Phase 1

The overall rate of confirmed SSI was 4.1%, based on the combination of methods (Table 2). An antimicrobial interval of ≥2 days identified 90% of infections, compared with diagnosis codes alone (48%) and routine surveillance (39%) (Table 3). Approximately 9% of patients met the antimicrobial drug exposure criterion, and 3.2% had one of the discharge diagnoses of interest (Table 3). The combination of antimicrobial drug exposure and diagnosis codes increased sensitivity slightly (96%) and was similar to antimicrobial drug exposure alone in predictive value and percentage of patients who met the criterion.

Phase 2

The overall infection rate was 5.5% (Table 2). The performance of the surveillance measures was similar to their performance in phase 1, in that an antimicrobial interval of ≥2 days identified substantially more infections (84%) than routine surveillance (38%, for the two hospitals that performed routine surveillance). Results of routine surveillance were comparable to those of antimicrobial drug exposure for deep incisional SSI (SSI rate of 0.3% for each), with superficial incisional SSI (0.3% vs. 1.3%) and endometritis (1.0% vs 2.6%), which accounted for the lower sensitivity of routine surveillance. In this phase, diagnosis codes (84% sensitivity) performed substantially better than routine surveillance and nearly as well as antimicrobial exposure. The positive predictive value to detect SSI was highest for diagnosis code–based screening (67%), and it was 37% for screening by antimicrobial drug exposure. The combination of antimicrobial exposure, diagnosis code–screening, or both improved sensitivity to 97% and had a positive predictive value similar to that of antimicrobial drug exposure alone.

As observed for CABG procedures, the proportions of patients who met screening criteria were similar for antimicrobial drug exposure alone (12.7%) and the combination of antimicrobial exposure and diagnosis codes (14.1%). A smaller proportion (6.4%) met only diagnosis code–screening criteria.

Breast Surgery Surveillance

Phase I

The overall confirmed SSI rate was 0.9%, based on the combination of all three methods (Table 2). Routine surveillance and antimicrobial drug exposure screening identified 71% of SSI (Table 3), compared with 50% for diagnosis codes. The combination of antimicrobial drug exposure and diagnosis codes identified 79%. The positive predictive value to detect SSI was highest for diagnosis code–based screening (58%), and was 19% and 20%, respectively, for screening by antimicrobial exposure and screening by a combination of antimicrobial drug exposure and diagnosis codes. The percentages of patients who met antimicrobial exposure criteria, diagnosis code criteria, and a combination are listed in Table 4.

Phase 2

The overall SSI rate, based on all three methods, was higher (2.2%) in this phase. Antimicrobial drug exposure was the most sensitive measure; it identified 94% of infections, compared with 70% for diagnosis codes and 33% for routine surveillance (two hospitals' data). The sensitivity of routine surveillance was similar for both deep and superficial infections.

The positive predictive value for detecting SSI was highest for diagnosis codes (79%); the positive predictive value was 33% for antimicrobial exposure alone and for the combination of antimicrobial drug exposure and diagnosis codes. The proportions of patients who met screening criteria were similar with antimicrobial drug exposure alone and the combination of antimicrobial exposure and diagnosis codes (6.7% and 6.8%, respectively), with a smaller proportion (2.0%) who met only diagnosis code–screening criteria.

Discussion

Many hospitals do not perform active SSI surveillance because it requires substantial resources. When hospitals do perform surveillance, our experience indicates that they often miss a substantial portion of infections. In the current study, many infections were missed after cesarean delivery and breast surgery, possibly because brief postoperative hospitalizations and infrequent readmissions for infection limited the efficiency of routine surveillance. The typical absence of microbiologic culture data associated with postcesarean endometritis may have also compromised the sensitivity of routine SSI surveillance after cesarean delivery. Furthermore, hospitals often cannot meaningfully compare their results with those from other hospitals because surveillance methods are not standardized. In contrast, surveillance based on antimicrobial drug exposure and diagnosis codes is objective and uses information that is collected routinely and is often available electronically. These factors may facilitate surveillance that performs uniformly over time and between institutions. We believe this method is likely to be widely applicable because the hospitals we studied had well-developed, independent surveillance programs and used a variety of different information technologies, yet all substantially improved their detection of SSI.

Overall, inpatient antimicrobial drug exposure was the best single measure for identifying SSI. We improved this measure's specificity by ignoring antimicrobial drugs administered on the operative and first postoperative days, when many patients receive perioperative antibiotic prophylaxis, and by omitting the large number of patients who received brief courses of antimicrobial drugs for other reasons. Even so, most patients identified by this method did not have conditions that met the CDC's SSI definitions. We previously observed that many of these patients without SSI are either "near misses," that is, they had signs and symptoms that prompted physicians to treat them as if they had an infection, or they had healthcare-associated infections at other sites (2). Therefore, above-threshold antimicrobial drug exposure can be a useful marker for clinically important postoperative illness that does not meet formal criteria for postoperative infection or for which documenting the medical record is insufficient to confirm a diagnosis.

In institutions such as the teaching and community hospitals in this study, infection control professionals will need to review from 4% to 20% of medical records to determine the SSI status for each patient who meets antimicrobial drug exposure or diagnosis code criteria, a percentage that is substantially lower than that required by routine surveillance. Moreover, confirming the status of each patient may not be necessary when the fraction of patients who meet the antimicrobial drug exposure criterion is within a stable range. Infection control professionals could reserve such assessments for instances when the elevation of this fraction above a specified threshold suggests the need for additional investigation.

The addition of diagnosis codes to antimicrobial drug–based surveillance improved sensitivity by 2% to 10%. Diagnosis codes improved screening for SSI after cesarean deliveries most markedly. In general, added sensitivity is likely not worth the extra effort currently required in most institutions to work with two different data sources. Screening for more codes might increase the sensitivity of this measure. The incremental value added by other types of information, such as microbiologic data, which have been studied by others (5,6), is unknown. Including such information, however, would add complexity to the process of acquiring and evaluating data. When additional automated data sources become widely available, the contribution they can make should be determined.

This study has several limitations. First, we may have missed some infections because we did not review the medical records from all patients or because the medical records had insufficient documentation. Second, before this surveillance method can be extended beyond these three surgical procedures, specific antimicrobial intervals will need to be evaluated for other procedures. Thus, additional studies are needed to assess the usefulness of this approach for other surgical procedures. Third, and perhaps most importantly, our studies did not address postdischarge surveillance for SSI, except when patients were readmitted to the same hospital. Therefore, assessment of inpatient antimicrobial drug exposure is only useful as a substitute or enhancement for traditional methods for detecting SSI among inpatients. The important problem of detecting postdischarge infections in patients who are not readmitted to the same hospital must be addressed through other means (e.g., through the use of automated claims data) (7).

To reduce the number of SSI, we need to better understand their occurrence in all hospitals that perform operations, which is not possible by using current surveillance methods. One way to perform standardized surveillance in all hospitals would be to use relatively simple, broad-based surveillance among inpatients by monitoring antimicrobial drug exposure, together with more intensive surveillance of hospitals that appear to have high infection rates not

explained by the difference in underlying patient risks for infection. Confirming a high case-mix adjusted infection rate would prompt evaluation of opportunities to improve policies, procedures, and training for personnel. Our studies indicate that monitoring inpatient antimicrobial drug exposure, possibly in combination with diagnosis codes for certain procedures, identifies more infections, requires fewer resources, and may be more easily standardized than conventional surveillance. These methods might replace conventional surveillance in some situations or, at a minimum, be used to focus valuable surveillance resources on patients most likely to have SSI.

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Enhanced Identification of Postoperative Infections among Outpatients

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We investigated using administrative claims data to identify surgical site infections (SSI) after breast surgery and cesarean section. Postoperative diagnosis codes, procedure codes, and pharmacy information were automatically scanned and used to identify claims suggestive of SSI ("indicators") among 426 (22%) of 1,943 breast procedures and 474 (10%) of 4,859 cesarean sections. For 104 breast procedures with indicators explained in available medical records, SSI were confirmed for 37%, and some infection criteria were present for another 27%. Among 204 cesarean sections, SSI were confirmed for 40%, and some criteria were met for 27%. The extrapolated infection rates of 2.8% for breast procedures and 3.1% for cesarean section were similar to those reported by the National Nosocomial Infection Surveillance program but differ in representing predominantly outpatient infections. Claims data may complement other data sources for identification of surgical site infections following breast surgery and caesarian section.

The most commonly used methods for surgical site infection (SSI) surveillance are labor intensive, susceptible to variability, and relatively insensitive to SSI after hospital discharge (1–17). Automated diagnosis and treatment information created during routine healthcare delivery, if sufficiently accurate, could be used to improve SSI detection. Surveillance based on full-text electronic medical records has outperformed more widely used methods (18,19), but currently these records exist for a minority of procedures. Diagnosis, procedure, and pharmacy codes associated with insurance claims are widely available but provide less detailed information. Nevertheless, claims data after coronary artery bypass grafting (CABG) identified 45% more SSI than did traditional surveillance (20). Claims data also allowed comparison of infection rates between hospitals (21). We investigated the utility of claims data after breast surgery and cesarean section for infection surveillance; these procedures are among the most commonly performed. Assessing different procedure types is important because differences in the duration of hospitalization, inpatient management, postdischarge care, and practices in billing and reimbursement that underlie claims data may vary substantially among different types of procedures.

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Methods

Breast Surgery

Automated Data

The study population was drawn from three different administrative claims systems within Harvard Pilgrim Health Care from July 1997 through February 1999 and one system of Tufts Health Plan from January 1996 through February 1999. All members had benefits that would be expected to generate inpatient and outpatient diagnosis and procedure claims; 90% of members also had pharmacy benefits (unpub. data). Breast procedures were identified by International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) or Current Procedural Terminology (CPT) procedure codes (online Appendix 1 available from http://www.cdc.gov/ncidod/eid/vol10no11/04-0784_app1.htm). Breast surgeries were divided into the following four categories on the basis of expected infection risk: 1) limited procedures, including reduction mammoplasty, mastopexy without implant, and mastectomy without axillary dissection or reconstruction; 2) procedures that involve implants; 3) mastectomy with

axillary dissection; and 4) procedures that include reconstruction. Breast biopsies and local excisions were not studied. The unit of analysis was procedure, and members could contribute more than one. However, procedures were excluded if another qualifying breast surgery occurred during the preceding or subsequent 60 days.

We searched claims and pharmacy data during the 60 days after surgery for previously published diagnosis codes, procedure codes, and antimicrobial agent dispensing suggestive of infection (21). Six categories of "SSI indicators" included diagnosis codes associated with inpatient, emergency department and outpatient settings, procedure codes for wound care in any setting, procedure codes for wound culture in any setting, and antimicrobial agents. The data available about antimicrobial drugs were limited to the outpatient setting. We then applied an algorithm that estimated the probability of infection on the basis of the presence or absence of SSI indicators in the six categories (21,22). The probability is derived from a logistic regression equation that assigns weights for each of the SSI indicator types for the individual patient. This probability could range from 0.006 for procedures with no SSI indicators to 0.998 for procedures with indicators of all six types.

Record Review

We reviewed records from all procedures with a predicted probability of infection >0.03. These constituted 96% of procedures with any SSI indicator. We obtained records from as many of the following as could be identified: the surgeon who billed for the initial procedure, the patient's primary care provider at the time of surgery, and full-text electronic ambulatory records (one claims system). For procedures with an indicator from a hospital or emergency department, we also contacted the institution that submitted the first such claim. From outpatient providers, we requested all notes during the 60 days after surgery, and from hospitals and emergency departments, we requested a discharge summary or progress notes. Initial requests were mailed, and providers who did not respond were telephoned 3–6 weeks later.

Full-text medical records were reviewed in two stages. A primary reviewer recorded the signs and symptoms during the 60 days after surgery that make up the National Nosocomial Infection Surveillance (NNIS) system definitions for SSI (4). If any signs or symptoms were found, an infectious disease physician experienced in clinical research performed a secondary review and classified the record as follows: 1) no signs or symptoms present, 2) some signs or symptoms of infection present without meeting the full NNIS definition, or 3) NNIS definition satisfied. The secondary reviewer also recorded the depth of SSI, if evident in the medical record. Discrepancies between primary and secondary reviews were resolved by two reviewers. The primary reviewer also determined whether or not the received records were adequate for inclusion in further analysis. Outpatient records were considered adequate if the record had notes for the 6 weeks after surgery, regardless of whether they contained specific reference to postoperative care or provided any explanation for the indicator that prompted the review. Hospital records were considered adequate if they contained notes from the identified admission or emergency department visit.

Completeness of Data

We compared the number of ambulatory claims, diagnoses associated with these claims, prescriptions before and after delivery, each SSI indicator type, and SSI confirmation rate among the four claims systems for each 6-month interval. The overall rate of SSI indicators and the confirmation rate for adequate records were not different. Small, but statistically significant, differences were noted among claims systems in patient age and the number of diagnoses on days with ambulatory claims. In one claim system, procedure codes for wound care were found after 5% of surgeries. This indicator type was associated with <1% of surgeries in the other three claims systems. The rates of procedure codes for wound culture and inpatient diagnosis codes were slightly different. A 10% drop over time occurred in the number of procedures with ambulatory claims in two systems, but this drop was not associated with a change in the rate of ambulatory diagnosis SSI indicators.

Analysis

We used the χ^2 test to compare categorical values and the Kruskal-Wallis tests for continuous variables. Analyses were performed with SAS (SAS, Cary, NC) for Unix version 8.2. We extrapolated the full SSI rate by multiplying the rate of confirmed infection among adequate charts by the proportion of procedures with a predicted probability of infection >0.03. We were prepared to compare infection rates among hospitals, but too few had a sufficiently high volume.

Cesarean Section

Automated Data

This study population comprised patients with ICD-9-CM procedure codes for cesarean section (online Appendix 1 available from http://www.cdc.gov/ncidod/eid/vol10no11/04-0784_app1.htm) and was limited to the three administrative claims systems at Harvard Pilgrim. Additional exclusion criteria were age <16 years or >50 years and sex recorded as male. Records were searched for 30 days postoperatively rather than 60 days, and the SSI

indicator list for cesarean section differed from that for breast procedures (online Appendix 2 available from http://www.cdc.gov/ncidod/eid/vol10no11/04-0784_app2.htm). These codes were chosen to identify SSI, including endometritis but not mastitis or urinary tract infection. We ignored SSI indicators associated with procedures having a diagnosis code suggestive of mastitis (mastitis indicators) (online Appendix 3 available from http://www.cdc.gov/ ncidod/eid/vol10no11/04-0784_app3.htm).

Record Review

We obtained records for procedures with an SSI or mastitis indicator, as described for breast procedures. For cesarean sections we requested records from all of the following that were applicable and available through claims: any obstetricians who performed the cesarean section, submitted the first outpatient claim with an SSI indicator, or was associated with most prenatal visits; the first hospital or emergency room that generated an SSI indicator; and full-text electronic ambulatory records (one claims system). Of received charts, the greatest portion (44%) came from the delivering obstetrician.

In addition to identifying SSI, the primary and secondary reviewers also assessed the presence of endometritis and mastitis by using the NNIS definitions (4). Only events occurring during the first 30 postoperative days were considered. Reliability between raters was assessed for the primary review ($\kappa = 0.86$ for identification of any sign or symptom, $\kappa = 0.62$ for identifying adequate charts).

Completeness of Data

We performed the same comparisons among claims systems for each 6-month period as was done for breast procedures. Differences occurred in patient age, number of prescriptions before and after surgery, and days with ambulatory claims. The differences in SSI indicators were less pronounced than those noted for breast procedures. The 10% decrease in ambulatory care claims over time was found for cesarean sections as well.

Analysis

In addition to the analyses described for breast procedures, we compared SSI rates among institutions with >150 procedures. We used logistic regression analysis to compare the proportions of cesarean sections with an SSI indicator at each hospital, adjusting for age (tertiles), secular trend (6-month intervals), and claims system. An interaction term "system*hospital" was tested to determine whether including data from multiple claims systems was appropriate when comparing hospitals' rates of SSI indicators.

Results

Breast Surgery

A total of 1,943 breast procedures were eligible (86% of all procedures identified). Most procedures had associated postoperative prescribing and ambulatory claims (Table 1). The most common SSI indicators were antimicrobial drug dispensing and ambulatory diagnosis codes; 22% of procedures had at least one indicator.

We requested records for 395 procedures (96% of those with an indicator) and received adequate documentation for 209 (53%) (Table 2). An infection was confirmed by NNIS criteria for 38 (18%); 28 (13%) had signs or

Table 1. Breast surgeries and cesarean sections identifiable from claims data[a]

Characteristics	Breast procedures	Cesarean section
No. of procedures	1,943	4,859
Median patient age in y (interquartile range)	48 (39–55)	32 (28–35)
% with prescriptions within 30 days after surgery	62	61
% with prescriptions in the 6 months before surgery	66	23
Postoperative days w/ambulatory claims[b]	6 (2–11)	1 (0–2)
Diagnoses on days w/ambulatory claims[b]	3 (2–4)	1 (1–2)
SSI indicator categories[c]		
Inpatient diagnosis (%)	30 (1.5)	63 (1.3)
Principally outpatient indicators (%)		
Ambulatory setting diagnosis (excludes ED)	173 (8.9)	112 (2.3)
Antimicrobial drugs in ambulatory setting	279 (14)	277 (5.7)
Wound culture	20 (1.0)	124 (2.6)
Wound care	33 (1.7)	11 (0.2)
Emergency department diagnosis	25 (1.3)	25 (0.5)
Any SSI indicator (%)	426 (22)	474 (10)

[a]SSI, surgical site infection, ED, emergency department.
[b]Postoperative days 0–60 for breast surgeries, 0–30 for cesarean section.
[c]Number of procedures (percent of total) with at least one SSI indicator of the listed type in the 60 days (breast procedures) or 30 days (cesarean sections) after surgery.

Table 2. Results of medical record review[a]

Characteristic	Breast (%)	Cesarean (%)
Procedures with possible SSI[b]	410 (21)	474 (10)
Requested 1 or more records (% of those with possible SSI)[c]	395 (96)	443 (93)
Records received (% of requested)	295 (75)	342 (77)
Adequate record received (% of requested)	209 (53)	255 (58)
No. among adequate records (% of adequate records)[d]		
Confirmed SSI	38 (18)	82 (32)
Some signs and symptoms of SSI, does not meet criteria	28 (13)	56 (22)
No evidence of SSI		
Another infection found, responsible for indicator	9 (4)	38 (15)
SSI indicator explained, not caused by infection	29 (14)	28 (11)
SSI indicator could not be explained	105 (50)	51 (20)

[a]SSI, surgical site infection.
[b]For breast procedures, those with possible SSI are procedures with predicted probability of infection >0.03. For cesarean section, procedures with possible SSI are those with any SSI indicator and no mastitis indicators.
[c]Common reasons for not requesting records were the following: member's information restricted, no provider could be identified from claims, or no current contact information could be obtained for a provider.
[d]Breast procedure outcomes based on 60 postoperative days; cesarean section outcomes based on 30 postoperative days.

symptoms that suggested infection without meeting the criteria. Among the 104 with records that included an explanation for the SSI indicator, 37% had a confirmed SSI, and 27% had signs or symptoms. Twenty (53%) confirmed infections were superficial; 12 (32%) were deep or in an organ space, and the depth could not be determined for 6 infections. Other infections or noninfectious causes explained the infection indicator for a minority of procedures, but in 50% of cases, neither the indicator nor a likely cause was mentioned.

Of the 38 infections we identified, 28 (74%) were identified during the first 30 days, which yielded an extrapolated infection rate based on NNIS (30-day) criteria of 2.8%. SSI indicators were found during a hospital admission for 40 (2.1%) of the 1,943 procedures, and SSI was confirmed for 20%, which yielded an inpatient extrapolated SSI rate of 0.4%. The similarly calculated outpatient SSI rate was 2.4%. Over the full 60 days reviewed, the infection rate was 3.8%.

The confirmation rate for patients with SSI indicators increased with the predicted probability of infection (Figure 1A), from 13% for those with a predicted probability <0.1 (76% of procedures with indicators) to 37% (13/35) for procedures with predicted probabilities of 0.4 to 0.5, and 50% for the 10 procedures with a predicted probability >0.8.

Among the four types of breast surgery, the occurrence of infection indicators ranged from 16% among limited procedures to 50% among procedures with reconstruction (Figure 2).The infection indicator type most responsible for this difference was antimicrobial agents, which were found after 41% of procedures with reconstruction but only 9% of limited procedures. The extrapolated 60-day infection rates among the four surgery types was 2.2% for limited procedures, 2.5% among procedures with implants, 5.2% among surgeries involving axillary dissection, and 5.5% among surgeries with reconstruction. Not enough hospitals had ≥100 procedures to allow comparisons.

Cesarean Section

A total of 4,859 (98% of those identified) cesarean sections were eligible. Antimicrobial drug prescribing was the most common SSI indicator, and 10% of deliveries had an indicator of some type (Table 1). One or more requests could be made for 443 (93%) cesarean sections, and adequate records were received for 255 (58%) (Table 2). SSI

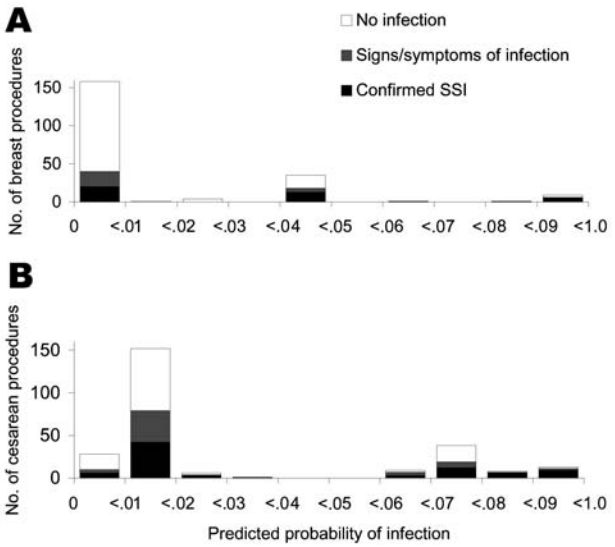

Figure 1. Infectious outcomes by predicted probability of surgical site infections (SSI) calculated from SSI indicators for A) breast procedures and B) cesarean sections. Shown are all procedures with adequate documentation, which excludes 80%–90% of procedures with no SSI indicator and predicted probability of infection at baseline, 0.006. Predicted probability of infection is based on the categories of SSI indicators found in claims and pharmacy records. The infectious outcomes for breast procedures are based on postoperative days 0–60; cesarean section outcomes are from days 0–30.

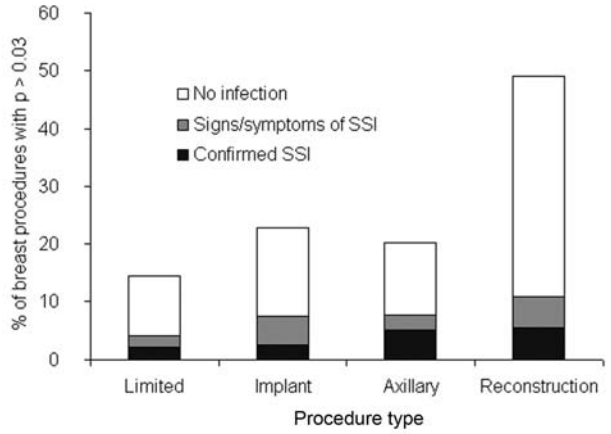

Figure 2. Infectious outcomes among four categories of breast procedure. Each bar represents all procedures with predicted probability of infection >0.03. Shown are 60-day outcomes extrapolated from the rates among procedures with adequate records. p, predicted probability of infection; SSI, surgical site infection; limited, reduction mammoplasty, mastopexy without implant, and mastectomy without axillary dissection or reconstruction; implant, breast procedures with an implant; axillary, breast procedures with axillary dissection; reconstruction, breast procedures with reconstruction.

were confirmed more often than for breast procedures: 82 deliveries (32% of those with adequate records) had a confirmed SSI, and another 56 (22%) had signs or symptoms. Among the 204 with records that included an explanation for the SSI indicator, 40% had a confirmed SSI, and 27% had signs or symptoms. Among confirmed SSI, 45% were superficial incisional, 6% were deep incisional, 24% were endometritis, and depth could not be determined for 24%. The extrapolated inpatient infection rate of 0.6% and the outpatient rate of 2.5% combine for an overall 3.1% 30-day SSI rate.

The distribution of predicted probability of infection among procedures with SSI indicators differed from that for breast procedures in having two discrete peaks (Figure 1B). Among the 73% of adequately documented procedures with predicted probability <0.4, the SSI confirmation rate was 28%. Above predicted probability 0.6 the confirmation rate was 44% (30/68).

Seven hospitals performed 150 or more cesarean sections. The proportion of each hospital's cesarean sections with an SSI indicator was 7.2%–14.8%, with confirmation rates that extrapolated to overall SSI rates of 1.6% to 6.7% (Figure 3). The hospitals' overall rates of confirmed SSI or signs and symptoms of SSI correlated with their rates of SSI indicators (p = 0.03). Three hospitals had an SSI indicator rate that was significantly greater than that of the hospital with the lowest SSI rate (hospital A in Figure 3), after adjusting for patients' age, claims system, and 6-month interval. We found no evidence of significant differences between claims systems in ranking hospitals.

Mastitis indicators were found after 22 deliveries, 15 of which also had an SSI indicator that would have identified them as "potential SSI" had they not been specifically excluded. Among the 14 for which an adequate record was obtained, 6 (43%) cases met the NNIS criteria for mastitis, and 5 (36%) had signs or symptoms of mastitis. None had a confirmed SSI.

Discussion

These findings support the major conclusion of earlier work with CABG procedures (20): claims data may be a useful adjunct to conventional surveillance for SSI. The strength of the claims data for breast procedures and cesarean delivery was in identifying SSI treated in the ambulatory setting, with >80% identified solely through ambulatory claims. In contrast, only 16% of SSI identified by NNIS occurred in the ambulatory setting (9). We believe claims data did not identify many of the SSI that occurred among inpatients because our overall extrapolated SSI rates were approximately equal to the rates published by NNIS during the period of this study. For breast procedures, the NNIS rate during the decade that included our study period was 2.1% (23), compared to our extrapolated rate of 2.8%. We note that the NNIS definition of breast procedure includes four less extensive procedures, including open biopsy and lumpectomy, that we did not study (24). For cesarean section, the 3.1% overall SSI rate identified by claims was almost identical to the 3.2% identified by NNIS for essentially the same procedures (23,24). The finding that claims data were apparently more useful

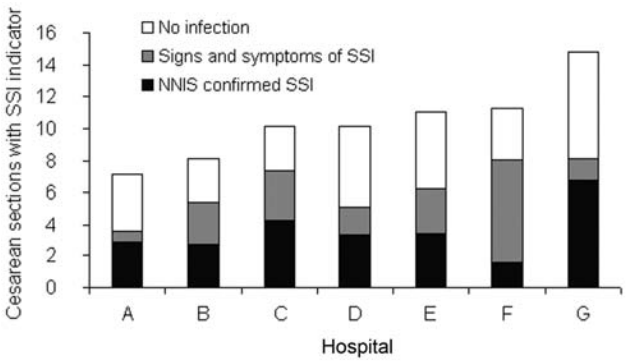

Figure 3. Hospital-specific infectious outcomes among cesarean sections with surgical site infection (SSI) indicators. Each bar represents all deliveries with potential SSI (n = 10–50), with outcomes extrapolated from those for whom adequate records were returned. The odds ratio (OR) (95% confidence interval) for a delivery having an SSI indicator at each hospital, adjusted for age, claims system, and 6-month interval, is as follows: Hospital A (reference), hospital B (OR 1.2 [95% CI 0.7–2.1]), hospital C (OR 1.7 [95% CI 1.0–2.9]), hospital D (OR 1.8 [95% CI 1.1–2.9]), hospital E (OR 1.7 [95% CI 1.0–2.8], hospital F (OR 1.7 [95% CI 0.9–3.1], hospital G (OR 2.3 [95% CI 1.3–4.0). NNIS, National Nosocomial Infections Surveillance; CI, confidence interval.

for identifying postdischarge SSI than inpatient SSI is a contrast to our finding in CABG procedures, that claims data appeared to identify SSI occurring in both inpatient and outpatient settings. The relative performance of claims data and routine inpatient surveillance would best be addressed by comparing results in the same institutions during comparable periods.

The overall rates at which SSI indicators identified true SSI were comparable to those we previously described for CABG procedures (21), if one applies the same criteria, considering only records that provided some explanation of the claims-based indicator (proportion with confirmed SSI or signs and symptoms: 63% for breast surgery, 68% for cesarean sections, 66% for CABG). The proportions of breast surgery and cesarean section patients whose records fully satisfied criteria for SSI were somewhat lower (37% and 40%) than was the case for our CABG population, for whom 53% of procedures with any indicator had a confirmed SSI (21). We believe these findings represent minimum estimates of the predictive value of the SSI indicators and of the extrapolated infection rates because many of the medical records we received did not identify the reason for the claim that yielded the SSI indicator or because the description of an abnormal surgical site contained too little detail to confirm an infection that may have been present. For CABG, the lower rates of procedures with signs and symptoms that did not fulfill all SSI criteria may have been attributable to more thorough documentation in the ambulatory medical records after CABG procedures.

The frequent dispensing of antistaphylococcal antimicrobial agents during the month after discharge, especially after 14% of breast procedures, bears consideration beyond its effect on lowering the predictive value of this SSI indicator. Much of this dispensing may have been for extended perioperative prophylaxis, a practice at variance with the Joint Commission for Accreditation of Healthcare Organizations' recent guideline limiting postoperative antimicrobial prophylaxis to a single day (25). As noted above, some of these antimicrobial courses may have been prescribed as treatment for diagnosed bacterial infections for which the documentation did not satisfy NNIS criteria or for presumed bacterial infections. Some courses may have been a prophylaxis regimen that would be considered inappropriate by current standards. Whatever the reasons, additional attention to postoperative antimicrobial drug use will be worthwhile, since if this use continues to be common, it may represent a large amount of currently undocumented illness or inappropriate antimicrobial drug use.

The predictive value of SSI indicators after cesarean section was reduced by the relatively common occurrence of infections at sites other than the surgical incision. Thus, these indicators may be useful in detecting postoperative infectious illness other than SSI. Also, for both breast procedures and cesarean sections, and in contrast to our experience with CABG procedures, the patients with an SSI indicator could be partitioned into groups with higher or lower likelihood of confirmed SSI.

We have no direct information about the status of approximately one quarter of patients with SSI indicators for whom no medical records could be obtained. Although we did not collect information systematically about missing records, most were likely missing for reasons unrelated to their clinical status, e.g., because the clinicians could not be contacted, the patients' records were no longer available, or because of the refusals of some institutions to provide records. While these missing patients may have had higher infection rates than the ones whose records we were able to review, we observed no important difference in the extrapolated infection rates between patients in one of the systems for which we obtained all requested ambulatory records because it used an electronic medical record system.

These results affirm the ability to combine data from multiple systems, which may be necessary to obtain enough information to estimate hospital-specific rates. The claims data for breast procedures from two health plans and the three administrative systems within one of those organizations were comparable in the proportion of procedures with most of the types of SSI indicators and in the rate at which identified procedures were confirmed to have an SSI. The higher rate of procedure codes for wound care in one data system probably represented a difference in coding practice or data structure. Claims systems do not need identical SSI indicator rates or confirmation rates for their data to be pooled, as long as this difference is controlled for when making other comparisons. Understanding whether a particular claims system is suitable for surveillance is important. For instance, if surgeons are paid a fixed price for a procedure and all postoperative care, then the claims are unlikely to provide indicators for ambulatory care. Similarly, antimicrobial indicators are much less meaningful if patients do not have a drug benefit or if the claims are "carved out," i.e., paid by another organization. Finally, for all data systems, routine checks should be performed for completeness, consistency, and accuracy of the data.

These claims-based indicators are not synonymous with infection and should not be used by themselves to categorize hospitals or practice groups as having high rates of complications. Instead, if additional evaluation supports the usefulness of claims data for this purpose, then these data might be used to identify a limited number of hospitals that merit additional follow-up to determine whether their rates of SSI are unusually high. The three hospitals with higher rates of SSI indicators after cesarean section

included the two with the highest extrapolated confirmed SSI rates, which suggests that focusing resources on understanding whether any of these three hospitals had increased rates because of remediable factors may have been effective. Valid reasons may exist for institutions' confirmed SSI rates to differ; for instance case-mix might differ. Additionally, any investigation of a specific hospital's indicator rate should begin by determining whether these elevated rates result from differences in the way claims for its patients are prepared or processed.

Widely available claims data, like those used here, may form the basis of an efficient system for identifying patients with increased likelihood of having had an SSI after breast surgery and cesarean section, as has been reported for CABG. If these results are confirmed, then assessing claims may be a useful adjunct to other forms of surveillance and might replace other methods for postdischarge surveillance.

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Mr. Miner is a medical student at University of Pennsylvania School of Medicine and during this project was a fellow in the Department of Ambulatory Care and Prevention at Harvard Medical School. He is interested in public health with a focus on the use of automated data for infection surveillance.

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Histopathologic Improvement with Lymphedema Management, Léogâne, Haiti

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In countries where bancroftian filariasis is endemic, lymphedema of the leg is a public health problem, particularly for women, who are disproportionately affected. We investigated the effect of basic lymphedema management (hygiene, skin care, and lower limb movement and elevation) on the histologic features of lymphedema. A total of 118 skin-punch biopsy specimens were collected from the legs of 91 patients enrolled in a lymphedema treatment clinic in Léogâne, Haiti. Follow-up biopsy specimens were collected from 27 patients ≈12 months later. Keratinocyte hyperproliferation, condensed dermal collagen, and mononuclear perivascular infiltrate increased with lymphedema stage, which suggested progressive chronic inflammation and fibrosis. Follow-up biopsies showed reductions in perivascular mononuclear infiltrate in the superficial dermis (41% decrease in prevalence), perivascular fibrosis in the deep dermis (58% decrease), and periadnexal mononuclear infiltrate (53% decrease). These data suggest that the clinical improvement commonly observed with basic lymphedema management has a histologic basis.

Lymphatic filariasis is an emerging disease in many areas of the tropics, where vector habitat has expanded because of large-scale water projects and declining sanitation associated with uncontrolled urban growth (1–3). In many countries where filariasis has been mapped systematically for the first time, its geographic distribution is much more extensive than previously believed (4,5). In Haiti, for example, the population at risk for infection was previously thought to be 1 million persons; however, the entire country (estimated population, 6–8 million) is now considered to be at risk (5).

Lymphedema of the limb is a physically deforming and socially stigmatizing consequence of filarial infection that affects ≈15 million persons worldwide (6). Although the factors responsible for the initiation and progression of filarial lymphedema to its most severe form, elephantiasis, have been debated, recurrent episodes of bacterial acute dermatolymphangioadenitis (ADLA) play a major role (7–9). Characterized by painful swelling of the limb, ADLA is accompanied by fever and chills lasting several days, sometimes with nausea and vomiting (7,8,10). As lymphedema progresses, the frequency of ADLA episodes generally increases (11,12). Skin changes of chronic lymphedema include thickening, nodular lesions, and pigmentary changes (13,14). Histopathologic studies have found evidence of inflammatory infiltrate in lymphedematous tissue (14,15).

Globally, lymphedema following infection with the filarial parasite *Wuchereria bancrofti* is more common in women than in men (6,16,17). In Haiti, the ratio of affected women to men is approximately 7 to 1 (16). Reasons for this discrepancy are unclear but may be related to differences in the "preferred" anatomic location of the adult filarial worm between men and women (18) and biologic factors, particularly pregnancy, that further stress the lymphatic system in women. Thus, in many filariasis-endemic areas, lymphedema is primarily a disease of women. Both the functional limitations caused by chronic lymphedema and the short-term impairment that accompanies episodes of ADLA compromise the ability of women to perform household chores and to participate in income-generating activities outside the home, which results in domestic and economic difficulties for their families and communities (19–24).

In 1998, the Global Program to Eliminate Lymphatic Filariasis embraced lymphedema management as a fundamental component of its strategy to eliminate lymphatic filariasis (25). Based on evidence of the bacterial etiology of ADLA, current World Health Organization (WHO)

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recommendations for management of lymphedema emphasize basic skin care and hygiene using soap, water, and antiseptics, as well as elevation of the leg, exercise, and proper footwear (26). Use of these measures improves skin condition, decreases the frequency of ADLA attacks, and reverses or arrests the progression of lymphedema, all of which improve quality of life (24,27–29).

Few studies in filariasis-endemic areas have examined stage-specific histologic changes in lymphedematous skin, and to our knowledge, no previous studies have examined histologic changes associated with WHO-recommended management of lymphedema. Our study attempts to characterize the histopathology of skin at different stages of lymphedema and assess histologic changes in the lymphedematous legs of patients enrolled in a lymphedema management program at Hôpital Ste. Croix in Léogâne, Haiti, an area where bancroftian filariasis is highly endemic.

Materials and Methods

Study Participants

The study protocol and consent forms were approved by the ethics committee at Hôpital Ste. Croix and the institutional review board at Centers for Disease Control and Prevention (CDC). Patients were eligible to participate if they were enrolled in the lymphedema treatment clinic at the hospital, had been examined by the clinic physician to rule out other causes of lower limb swelling, gave informed consent to collection of all biopsy specimens, had no medical contraindications to biopsy, had no ADLA episodes during the previous 2 weeks, and lived within a 10-km radius of the hospital.

Patients were tested for filarial infection by using an immunochromatographic card test (ICT), which detects antigen of adult *W. bancrofti* in the blood (30). Lymphedema stage was assessed by using an adaptation of a three-stage system recommended by WHO (31). Stage 1 lymphedema is characterized by swelling that is reversible on elevation at night. Stage 2 lymphedema is not reversible upon elevation and has no papillomatous changes. Stage 3 lymphedema, sometimes called elephantiasis, is characterized by papillomatous lesions and pronounced dermatosclerosis.

Patients were instructed in lymphedema self-care (27), with emphasis on thorough daily washing of the limb, basic skin care to treat and prevent entry lesions, range-of-motion limb exercises, and elevation of the leg during the day when possible and at night while sleeping. Participants were provided with basic supplies (e.g., soap, towels, wash basin) as needed. To monitor lymphedema self-care, patients returned to the clinic or were visited at home every 4–6 weeks and were asked about compliance with the regimen since the previous visit. Patients were encouraged to seek antimicrobial drugs and symptomatic treatment at the hospital during ADLA attacks. Thus, most ADLA attacks were observed by clinic staff; a few attacks were recorded on the basis of patient history and the presence of residual clinical signs (e.g., peeling of the skin, swelling) at the next follow-up visit.

Biopsy and Analysis

A total of 91 patients agreed to undergo skin-punch biopsy of their lymphedematous leg or legs, and 26 of these patients also agreed to a biopsy of their non-lymphedematous leg (control). Twenty-seven patients agreed to have follow-up biopsies of their lymphedematous limb ≈12 months later. Biopsy specimens were taken from the anterolateral surface of the leg from a site that was representative in appearance of the rest of the leg. Irregular protrusions and skin lesions were avoided. After the skin was cleaned with betadine and anesthetized with 1% lidocaine, a 4-mm skin-punch biopsy specimen was obtained, and suture or 3M Steri-Strips were used to close the skin at the biopsy site. A short course of oral amoxicillin (250 mg three times a day for 5 days) was given to help prevent bacterial infection.

Skin-punch biopsy specimens were fixed in formalin in Léogâne, Haiti, and sent to CDC in Atlanta, Georgia, where they were embedded in paraffin. Five-micrometer sections were cut and stained with hematoxylin and eosin. All biopsy sections were read by the same pathologist (JG), who was blinded with respect to patient identification, lymphedema stage, and whether the specimen was from an initial or follow-up biopsy. Each biopsy specimen was evaluated for the presence or absence of the histopathologic characteristics presented in Table 1.

Statistical Analysis

Statistical analysis was performed using EpiInfo 6.0. The chi-square and Fischer exact tests were used to compare differences in the proportions of specimens with histopathologic features.

Results

Participants

Of the 91 patients enrolled in this study, 73 (80%) were female. Women and men did not differ significantly with regard to age, lymphedema stage, or histologic features (data not shown). Median age was 39 years (range 16–75 years). One patient had bilateral lymphedema; the others had unilateral disease. Two patients had filarial antigen detected in the blood by ICT. Both were treated with diethylcarbamazine, the drug of choice for *W. bancrofti* infection. The median length of time between enrollment

Table 1: Histopathologic features evaluated in skin biopsy specimens from patients with lymphedema of the leg, Léogâne, Haiti

Location, feature	Comments
Epidermis	
Hyperkeratosis	Thickening of horny layer, with disappearance of basket-weave pattern.
Hypergranulosis	Basophilic pyknotic nuclei in keratin layer.
Acanthosis	Increase in thickness of the stratum malpighii.
Superficial dermis	
Fibrolamellar hyperplasia	Distinct collagen bundles parallel to basal epidermal layer.
Condensed collagen	Thickened and closely packed collagen bundles with deep eosinophilic staining pattern.
Perivascular fibrosis	Condensed collagen concentric to vessels.
Perivascular infiltrate	Cellular infiltrate surrounding vessels, defined as either acute (presence of neutrophils or eosinophils) or chronic (presence of mononuclear inflammatory cells, including lymphocytes and macrophages).
	Intensity of chronic infiltrate was noted as mild (average of ≤5 lymphocytes or macrophages observed in 40x magnification viewing field of perivascular spaces) or pronounced (average of >5 lymphocytes or macrophages), based on examination of several fields per slide.
	Plasma cells noted.
Deep dermis and subcutaneous tissue	
Perivascular fibrosis	Same as in superficial dermis.
Perivascular infiltrate	Same as in superficial dermis.
Periadnexal infiltrate	Cellular infiltrate around hair, sweat, and sebaceous glands. Type and intensity were noted as previously defined for the superficial dermis.
Infiltrate in subcutaneous tissues	Cellular infiltrate in fibrous septa among adipose tissue. Type and intensity were noted as previously defined for superficial dermis.

in the lymphedema management program and the first biopsy was 21 days (range 0–866 days).

Microbial Findings

No clinical signs of infection or inflammation were evident at the biopsy site. Microscopic examination of tissue sections stained with hematoxylin and eosin revealed no evidence of bacterial infection and no *W. bancrofti* adult worms or microfilariae.

Initial Biopsy Specimens and Histopathologic Features

One hundred eighteen biopsy specimens were collected, 92 from lymphedematous legs and 26 from nonlymphedematous control legs. Biopsy specimens were collected a median of 14 cm (range 5–20 cm) above the sole of the foot. The number of biopsy specimens taken from control legs and from legs with stage, 1, 2, or 3 lymphedema was 26, 12, 60, and 20, respectively. No postoperative infections developed. Among the biopsy specimens, the proportion with histopathologic features (prevalence) increased with lymphedema stage (Table 2).

Epidermis

The prevalence of hyperkeratosis, hypergranulosis, and acanthosis increased significantly with stage of lymphedema. Hyperkeratosis was the predominant pathologic feature within the epidermis, regardless of stage, and was found in 80% of biopsy specimens from legs with stage 3 lymphedema. No biopsy specimens from unaffected control legs showed hypergranulosis or acanthosis.

Superficial Dermis

Within the superficial dermis, the prevalence of fibrolamellar hyperplasia increased from 19% in nonlymphedematous legs to 50% in stage 1 lymphedema but remained similar for stages 1–3. The prevalence of condensed collagen steadily increased from 0% in unaffected control legs to 30% in stage 2 lymphedema ($p = 0.002$). Most of the perivascular infiltrate in the superficial dermis was composed of mononuclear cells, primarily lymphocytes and macrophages. Plasma cells were found only in stage 2 and 3 lymphedema and were significantly less common in biopsies from women (4 [4%] of 93) than from men (7 [28%] of 25) ($p = 0.002$). The prevalence of chronic mononuclear infiltrate increased steadily from 42% in nonlymphedematous biopsy specimens to 95% in stage 3 biopsy specimens ($p = 0.0002$). In all areas where cellular infiltrate was observed, lymphocyte and macrophage cell populations were assessed together with respect to infiltrate intensity because activated lymphocytes were difficult to differentiate microscopically from macrophages. The prevalence of pronounced lymphocyte and macrophage infiltrate increased with lymphedema severity: 4% of biopsies from nonlymphedematous legs had pronounced infiltrate compared to 35% of stage 3 biopsy specimens ($p = 0.008$).

Deep Dermis

Perivascular fibrosis was recorded in 27% and 40% of skin biopsy specimens from patients with stage 2 and stage 3 lymphedema, respectively; it was more prevalent within

Table 2. Number and percentage of initial skin biopsy specimens in which histopathologic features were detected, by stage of lymphedema, Léogâne, Haiti

Location in skin	Histopathologic characteristic	Control (N = 26) n (%)	Lymphedema Stage 1 (N = 12) n (%)	Lymphedema Stage 2 (N = 60) n (%)	Lymphedema Stage 3 (N = 20) n (%)
Epidermis	Hyperkeratosis	4 (15)	5 (42)	23 (38)[a]	16 (80)[b]
	Hypergranulosis	0 (0)	1 (8)	5 (8)	4 (20)[a]
	Acanthosis	0 (0)	3 (25)[a]	11 (18)[a]	6 (30)[c]
Superficial dermis	Fibrolamellar hyperplasia	5 (19)	6 (50)	25 (42)[a]	11 (55)[a]
	Condensed collagen	0 (0)	1 (8)	18 (30)[c]	7 (35)[c]
	Perivascular fibrosis	0 (0)	1 (8)	6 (10)	3 (15)
	Perivascular infiltrate				
	Acute	0 (0)	0 (0)	2 (3)	0 (0)
	Chronic	11 (42)	8 (67)	46 (77)[c]	19 (95)[b]
	Pronounced intensity	1 (4)	2 (17)	11 (18)	7 (35)[c]
	Presence of plasma cells	0 (0)	0 (0)	9 (15)[a]	6 (30)[c]
Deep dermis	Perivascular fibrosis	3 (11)	1 (8)	16 (27)	8 (40)[a]
	Perivascular infiltrate				
	Acute	0 (0)	0 (0)	0 (0)	0 (0)
	Chronic	12 (46)	6 (50)	54 (90)[b]	19 (95)[b]
	Pronounced intensity	1 (4)	3 (25)	20 (33)[c]	11 (55)[b]
	Presence of plasma cells	1 (4)	7 (58)[b]	37 (62)[b]	15 (75)[b]
	Periadnexal infiltrate				
	Acute	0 (0)	0 (0)	0 (0)	0 (0)
	Chronic	4 (15)	4 (33)	36 (60)[b]	11 (55)[c]
	Pronounced intensity	0 (0)	0 (0)	10 (17)[a]	3 (15)
Subcutaneous tissue	Infiltrate in fibrous septa				
	Acute	0 (0)	0 (0)	0 (0)	0 (0)
	Chronic	1 (4)	3 (25)	19 (32)[c]	9 (45)[c]
	Pronounced intensity	1 (4)	3 (25)	5 (8)	3 (15)

[a]$p < 0.05$ (compared to control leg biopsy specimens).
[b]$p < 0.001$ (compared to control leg biopsy specimens).
[c]$p < 0.01$ (compared to control leg biopsy specimens).

the deep dermis than the superficial dermis at nearly every stage of lymphedema. The prevalence of perivascular infiltrate, composed entirely of mononuclear cells, increased from 50% in stage 1 lymphedema to 90% in stage 2 ($p = 0.003$). Pronounced chronic infiltrate and plasma cells were also more common in the deep dermis than in the superficial dermis at every stage of lymphedema. The prevalence and intensity of periadnexal infiltrate, all of which was mononuclear, increased with stage of lymphedema. Plasma cells were rarely observed in periadnexal infiltrate.

Subcutaneous Tissue

All cellular infiltrate in fibrous septa surrounding subcutaneous adipose tissue was mononuclear, and its prevalence increased with lymphedema stage, particularly between nonlymphedematous controls and stage 1 lymphedema (4% to 25%). Plasma cells were rarely observed in the infiltrate surrounding subcutaneous tissue.

Follow-up Participants and Biopsy Specimens

Follow-up biopsy specimens were collected from the lymphedematous limb of 27 patients a median of 365 days (range 317–656 days) after their first biopsy. Of these 27 patients, 20 (74%) were women; the median age was 38 years (range 16–61 years). They did not differ significantly by sex, age, or lymphedema stage from the 64 participants who only had one skin biopsy.

Compliance with self-care practices during the interval between biopsies was high. At 96%, 94%, 87%, and 98% of monthly follow-up visits, respectively, patients reported that, since the previous visit, they had washed the leg daily, practiced range-of-motion exercises, elevated the leg during the daytime, and raised the foot of the bed at night. No changes in lymphedema stage were observed.

The second biopsy specimen was obtained a median of 14 cm (range 6–17 cm) above the sole of the foot, and a median of 1 cm (range <1–5 cm) from the first biopsy site. No postoperative infections developed. Of the 27 biopsy specimens that were collected for follow-up, 2 were from legs with stage 1 lymphedema, 18 from stage 2 lymphedema, and 7 from stage 3 lymphedema.

Of the 27 patients, 21 (78%) had reported one or more ADLA attacks during the 12-month period before entering the program. In contrast, only eight (30%) reported one or more attacks during the interval between biopsies (1, 4, and 3 patients with stage 1, 2, and 3 lymphedema, respectively). The mean reported incidence of attacks during the

year before entering the program was 1.7 (range, 0–8) per person-year, compared to 0.5 (range, 0–3) observed between biopsies (p = 0.0009).

Histopathologic Changes with Lymphedema Management

The prevalence and intensity of histopathologic abnormalities tended to be greater in initial skin biopsy specimens (Figure 1A, B, and C) than in follow-up biopsy specimens (Figure 1D, E, and F) (Table 3). Hyperkeratosis and hyperplasia of the epidermis were more prominent on initial specimens (Figure 1A) than on follow-up specimens (Figure 1D). The thick collagen bundles observed in the dermis of initial biopsy samples (Figure 1A) were less obvious in samples after 1 year of lymphedema management (Figure 1D). In the superficial dermis, substantial decreases were observed between the first (Figure 1B) and second (Figure 1E) biopsies, both in the prevalence of chronic perivascular infiltrate (100% to 59%, p = 0.0002, Table 3) and in the proportion of specimens with pronounced infiltrate intensity (37% to 11%, p = 0.03).

Perivascular fibrosis in the deep dermis was less common in follow-up biopsy samples (22%, Figure 1E) than in initial samples (52%, Figure 1B). Additionally, significant decreases were observed in the prevalence of chronic periadnexal infiltrate (70% to 33%, p = 0.007) and the percentage of specimens with pronounced infiltrates of lymphocytes and macrophages in periadnexal areas of the deep dermis (26% to 0%, p = 0.005, Table 3, and Figures 1C and F). The replacement of thick collagen bundles around adnexi in the first specimen (Figure 1C) with adipose cells in the second specimen (Figure 1F) was also noted in the subcutaneous tissue.

Figure 2 summarizes the histologic changes in each of the 27 patients with follow-up biopsies. Histopathologic regression or improvement was defined as the disappearance of a histopathologic characteristic on follow-up specimen, while histopathologic progression or worsening was defined as the appearance of a previously unnoted histopathologic characteristic on follow-up specimen. All but one patient (96%) showed histopathologic regression in one or more characteristics. Histopathologic improvement was observed among all stages of lymphedema. However, 4 (57%) of 7 legs with stage 3 lymphedema showed regression of chronic perivascular infiltrate in the deep dermis, compared to none of 20 legs with stage 1 or 2 lymphedema (p = 0.003). Eleven (41%) patients showed regression in four or more characteristics; they did not differ significantly from the other 16 patients with respect to sex, age, stage, or duration of lymphedema; duration of participation in the lymphedema program before the first biopsy; interval between biopsies; or ADLA incidence between biopsies (Table 4). Sixteen (59%) patients showed histopathologic progression in one or more characteristics. None of the 27 patients had progression of chronic perivascular infiltrate.

Discussion

The physical, personal, social, and economic difficul-

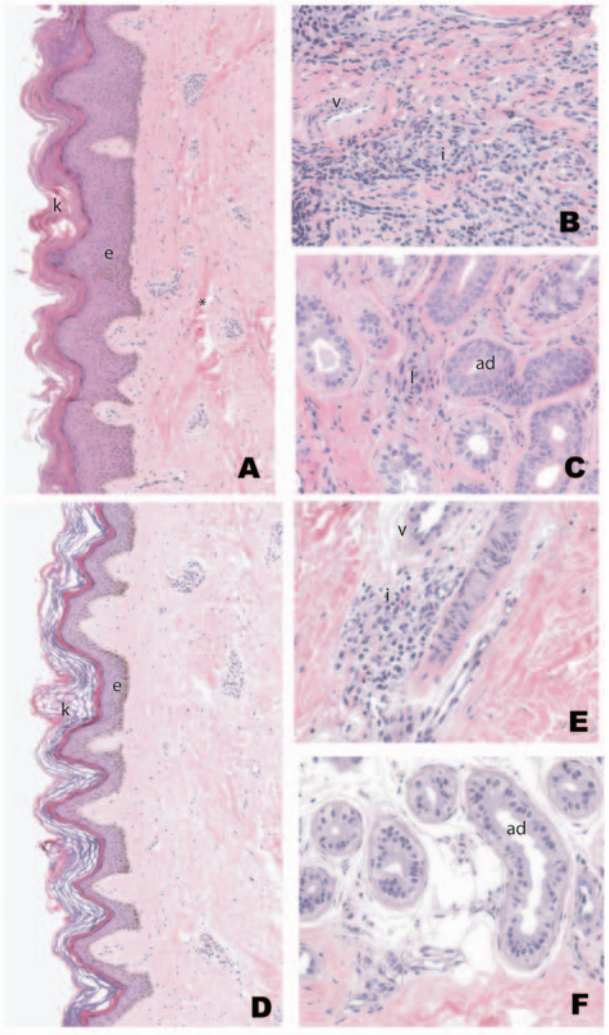

Figure 1. Representative sample of skin punch biopsy specimens from patients with lymphedema before (A, B, C) and after (D, E, F) 1 year of basic lymphedema management. Pretreatment abnormalities of the epidermis (e), which include increased number of epithelial cells (acanthosis and epidermal hyperplasia) and thickening of the keratin (k) layer, were improved after treatment (compare first [A] and second [D] biopsy specimens from same patient). Also noted is thickening of collagen bundles (*) in the dermis on the first (A) sample, which is not observed on the second (D). The intensity of inflammatory cells (i), which stain blue, surrounding fibrosed vessels (v) on the first sample (B), are more prominent than in the second sample (E). The amount of inflammation (i) in the subcutaneous adipose tissue is also more pronounced in the first biopsy sample (C) than the second sample (F) where adnexa (ad) with minimal inflammation can be observed. (Hematoxylin and eosin stains; original magnification for A, C, D, and F = 25x; B and E = 50x.)

Table 3. Number and percentage of skin biopsy specimens in which histopathologic features were detected in 27 patients practicing lymphedema management, Léogâne, Haiti[a]

Location in skin	Histopathologic characteristic	1st biopsy (N = 27) n (%)	2nd biopsy (N = 27) n (%)	p value
Epidermis	Hyperkeratosis	14 (52)	12 (44)	0.59
	Hypergranulosis	5 (18)	1 (4)	0.09
	Acanthosis	7 (26)	3 (11)	0.16
Superficial dermis	Fibrolamellar hyperplasia	16 (59)	11 (41)	0.18
	Condensed collagen	10 (37)	5 (18)	0.13
	Perivascular fibrosis	4 (15)	1 (4)	0.17
	Perivascular infiltrate			
	Acute	0 (0)	0 (0)	
	Chronic	27 (100)	16 (59)	0.0002
	Pronounced intensity	10 (37)	3 (11)	0.03
	Presence of plasma cells	7 (26)	4 (15)	0.31
Deep dermis	Perivascular fibrosis	14 (52)	6 (22)	0.02
	Perivascular infiltrate			
	Acute	0 (0)	0 (0)	
	Chronic	25 (93)	21 (78)	0.12
	Pronounced intensity	9 (33)	6 (22)	0.37
	Presence of plasma cells	18 (67)	18 (67)	1
	Periadnexal infiltrate			
	Acute	0 (0)	0 (0)	
	Chronic	19 (70)	9 (33)	0.007
	Pronounced intensity	7 (26)	0 (0)	0.005
Subcutaneous tissue	Infiltrate in fibrous septa			
	Acute	0 (0)	0 (0)	
	Chronic	10 (37)	10 (37)	1
	Pronounced intensity	5 (18)	1 (4)	0.09

[a]For each patient, the second biopsy specimen was taken near the same site on the same lymphedematous leg ≈1 year after the first biopsy.

ties caused by lymphedema and elephantiasis of the leg in many filariasis-endemic areas disproportionately affect women (6,16,17,21,24). Filariasis elimination programs' increasing adoption of simple, inexpensive measures for lymphedema management has led to reduced ADLA incidence, reduced lymphedema-related illness, decreased stigma, and improved quality of life for women in many filariasis-endemic areas (24,27–29,32). Our study complements these findings by providing evidence of histologic improvement in patients who routinely practice lymphedema self-care.

Increasing lymphedema stage was associated with increased proliferation of keratinocytes and acanthosis in the epidermis and with an increased prevalence of fibrolamellar hyperplasia, condensed collagen, perivascular fibrosis, and perivascular and periadnexal infiltrate in the dermis. Epidermal hyperproliferation, which has been described previously for lymphedema in filariasis-endemic areas (14), can result from an influx of macrophages that release epidermal growth factors in response to repeated irritation caused by foreign antigens within the skin.

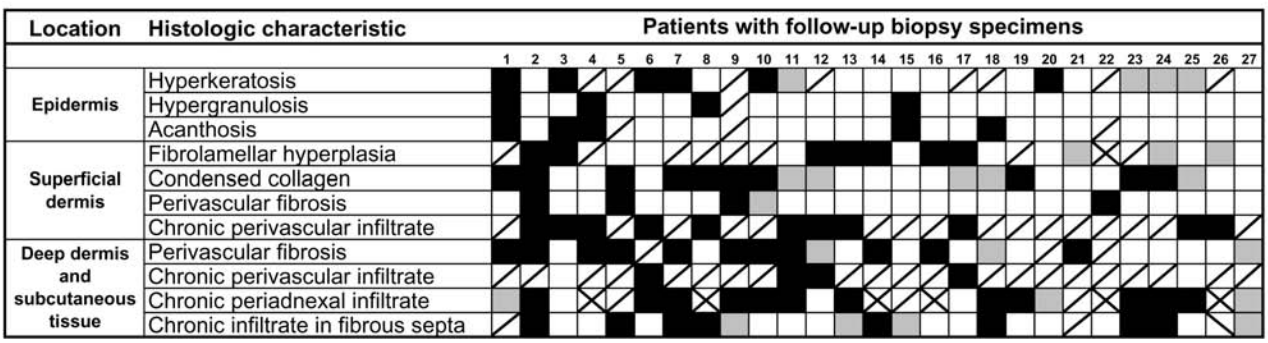

Figure 2. Individual histologic responses of the 27 patients with follow-up biopsy specimens who participated in a lymphedema management program for ≈1 year. Black boxes indicate histopathologic regression or improvement, gray boxes indicate histopathologic progression or worsening, white boxes indicate the absence of histopathologic changes in either biopsy specimens, and boxes with a diagonal line indicate that histopathologic changes were observed on both initial and follow-up biopsy specimens. Boxes with an X indicate insufficient data.

Table 4. Demographic, physical, and treatment-related characteristics of 27 patients with initial and follow-up skin biopsy specimens, by degree of histologic improvement (involving ≥4 vs. <4 histologic characteristics), Léogâne, Haiti

Factors examined	Improvement in ≥4 histologic characteristics	Improvement in <4 histologic characteristics
Number of patients	11	16
Female (%)	9 (82)	11 (69)
Median age, y (range)	39 (20–61)	32 (16–61)
Stage of lymphedema (%)		
Stage 1	2 (18)	0 (0)
Stage 2	5 (45)	13 (81)
Stage 3	4 (36)	3 (19)
Median no. of days in lymphedema management before 1st biopsy (range)	21 (0–432)	19.5 (0–468)
Median no. of days between biopsies (range)	359 (317–503)	366 (317–656)
Median annual incidence of ADLA between biopsies (range)	0 (0–2)	0 (0–3)
Median duration of lymphedema, y (range)	11.5 (4–27)	7 (0–25)

The condensed collagen bundles and perivascular fibrosis in our biopsy specimens help explain the hardness of the skin in persons with stage 3 lymphedema. We observed a progression from thin, lacelike dermal collagen in biopsy samples from legs with no lymphedema to fibrolamellar hyperplasia in the rete ridges accompanied by thick condensed collagen bundles in patients with severe lymphedema. In some cases, these collagen bundles encased vascular vessels as well as adnexal structures. Lymph stasis, which results from lymphatic dysfunction, leads to accumulation of blood proteins, cellular metabolic products, and recirculating lymphocytes in the tissue (33). The presence of these molecules and cells has been shown to induce epidermal thickening, deposition of collagen in the dermis, and proliferation of fibroblasts (33,34).

The prevalence of mononuclear inflammatory cells around vessels and adnexa and in the fibrous septa also increased with lymphedema stage. The inflammatory infiltrate consisted predominantly of lymphocytes and macrophages, similar to what has been previously reported (14,15). The high frequency of plasma cells in the deep dermis, present in nearly 60% of stage 1 biopsy specimens, was unusual and has not been previously reported in patients with lymphedema in filariasis-endemic areas. Plasma cells are infrequently found in healthy skin and are generally associated with chronic inflammation or bacterial infections (35). The dramatically higher number of plasma cells within the deep dermis suggests a more pronounced immunologic response than in the superficial dermis.

The stimulus for chronic mononuclear infiltrate within the superficial and deep dermis in these patients is unknown. Chronic infiltrate may have resulted from poor clearance by the lymphatic system of bacteria penetrating the skin surface or a prolonged immune response following an ADLA attack. Chronic inflammation might also be provoked by the presence of macromolecules, the production of cytokines and growth factors, and their accumulation in the skin. Studies in filariasis-endemic areas have shown proinflammatory immune proteins and cytokines in the serum and lymph fluid of patients with lymphedema (34).

The fact that specimens from some nonlymphedematous legs had histologic abnormalities, especially chronic perivascular infiltrate, has several possible explanations. First, these abnormalities may have been due to minor leg trauma (i.e., cuts and bruises) or interdigital fungal infections (27). Of 11 biopsy specimens from nonlymphedematous legs that had perivascular lymphocytes and macrophages in the superficial dermis, only 1 (9%) showed pronounced infiltrate. Second, stage 1 lymphedema may have been misclassified as nonlymphedematous in some cases. Finally, subclinical damage may have already been present in the legs that appeared normal.

A trend toward improvement was noted for virtually all histologic characteristics examined in the follow-up biopsy specimens. The marked improvement in cellular infiltrate in the superficial dermis is consistent with the effect of improved skincare and hygiene. In addition, the prevalence and intensity of chronic cellular infiltrate surrounding adnexa were significantly reduced during the 1-year period. Taken as a whole, these observations are consistent with the hypothesis that basic lymphedema management, which reduced microbial load on the skin surface and healed entry lesions, led to a decrease in ADLA incidence and a reduction in chronic inflammation of the skin.

No changes were observed in lymphedema stage despite reductions in skin inflammation and fibrosis; however, the three-stage classification system for lymphedema provides only a gross assessment of clinical status. A seven-stage system with better discriminating power (27), developed after this study was completed, is currently being used in filariasis-endemic areas.

At an individual level, we found no factors, including the absence of ADLA attacks, that were significantly asso-

ciated with histopathologic regression. This finding may be attributed to the limited number of persons in each group, the prompt use of antimicrobial drugs after onset of ADLA symptoms, or variation in inflammatory responses among persons. Acute histologic responses to a single ADLA attack may have been transient, so that by the time of the second biopsy, histologic markers of the episode had cleared.

This study has several limitations. First, no control group was included, since ethical considerations precluded collecting follow-up biopsies from persons not instructed in lymphedema self-care. However, we would not have expected to observe significant histopathologic improvement in the absence of intervention. Second, we did not use special stains for bacteria or immunohistochemical assays for subtyping cells and collagen, all of which would be useful for understanding the pathogenesis of lymphedema and are currently planned. Third, the interval between initiating lymphedema self-care and the first biopsy varied among patients; the first biopsy specimens was not always a "baseline" specimen. However, this variation did not appear to influence the degree of histologic improvement during follow-up, which suggests that the benefits of lymphedema management are not limited to the first few months but continue to accrue with practice. Finally, the number of patients included in the follow-up study was small, which limited statistical power. Larger studies, preferably involving several centers, are recommended.

In conclusion, participation in a lymphedema management program for 1 year was associated with significant reductions in cellular infiltrate and fibrosis. Lymphedema management, based on inexpensive and practical elements of self-care at home, can lead not only to histologic improvement, as shown here, but also to clinical and functional benefits and to improved quality of life. Programs in Brazil (27), India (29), Haiti (24,32), Guyana (28), and elsewhere have documented these benefits and pioneered creative ways, such as support groups (32), to teach affected women the principles of lymphedema self-care and motivate them to continue to practice it. In most filariasis-endemic areas, however, such programs do not yet exist. To reach the millions of women who suffer from this disease, lymphedema management must be expanded, as an integral part of the Global Program to Eliminate Lymphatic Filariasis, to all major filariasis-endemic areas worldwide.

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Nucleocapsid Protein as Early Diagnostic Marker for SARS

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Serum samples from 317 patients with severe acute respiratory syndrome (SARS) were tested for the nucleocapsid (N) protein of SARS-associated coronavirus, with sensitivities of 94% and 78% for the first 5 days and 6–10 days after onset, respectively. The specificity was 99.9%. N protein can be used as an early diagnostic maker for SARS.

Early laboratory diagnosis of the severe acute respiratory syndrome–associated coronavirus (SARS-CoV) is one step in preventing recurrence of a global outbreak. The availability of the complete genomic sequence of SARS-CoV has facilitated the development of a variety of diagnostic tests for SARS (1). Reverse transcription–polymerase chain reaction (RT-PCR) has been used as a rapid diagnostic test in most of the research centers during the last epidemic (2–6). However, early diagnosis of SARS remains a problem for nonresearch laboratories with little experience in molecular testing. We have developed an antigen-capture enzyme-linked immunosorbent assay (ELISA) based on monoclonal antibodies against the nucleocapsid (N) protein of SARS-CoV (7), a predominant antigen produced in the infected cell-culture filtrate. High levels of circulating N protein can be detected in the serum samples of patients with SARS. We attempt to demonstrate the temporal profile of the N protein and antibodies in serum samples from a large cohort of patients with SARS during the acute and convalescent phases of the disease. Our findings suggest that detecting N protein in serum can be used as an early diagnostic marker for SARS.

The Study

During the 2003 SARS epidemic in Guangzhou, 420 serum specimens were collected from 317 patients 1–90 days after the onset of symptoms. The condition of all patients was diagnosed according to the World Health Organization criteria and confirmed by seroconversion or a fourfold increase in antibody titer against SARS-CoV by means of immunofluorescent testing. The N protein–capture ELISA was performed (7). Briefly, 100 µL of serum was added to the wells of a microtiter plate coated with a mixture of three anti-N protein monoclonal antibodies, and the plates were incubated at 37°C for 60 min. After the plates were washed, 100 µL of anti-N rabbit antiserum was added to the wells, and the plates were incubated at 37°C for 60 min. The wells were washed again and incubated for 1 h at 37°C with 100 µL of peroxidase-conjugated goat anti-rabbit immunoglobulin (Ig)G . After the plates were washed, 100 µL of tetramethylbenzidine solution was added to each well. The experiments involving the use of serum samples from patients with SARS were performed within the safety cabinet of a biosafety level 2 laboratory.

The results for the 420 serum specimens tested by the N protein–capture ELISA are shown in Figure 1. The N protein could be detected as early as day 1 and until day 18. In the 146 serum samples positive for N protein, the optical density (OD) value was highly variable from one sample to another on the same day. The sensitivity of detection was 94% (80 of 85 patients) with blood samples taken during the first 5 days and 78% (47 of 60 patients) for samples taken 6–10 days after onset of symptoms. The detection rate of N protein decreased to 27% on days 11–20 after onset of symptoms. Serum N protein was

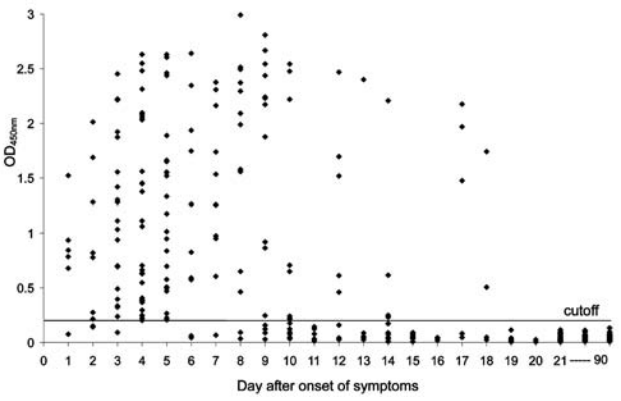

Figure 1. N protein detection in 420 serum samples from 317 patients with severe acute respiratory syndrome (SARS). Data represent the optical density at 450 nm (OD_{450}) of undiluted serum samples. To establish the normal range of the N protein–capture enzyme-linked immunosorbent assay, serum specimens from 400 healthy blood donors were analyzed. The mean OD_{450} for these specimens, as determined by the assay, was 0.078, with a standard deviation of 0.023. The cutoff OD_{450} of the assay was then calculated as follows: cutoff = mean of OD_{450} from 400 normal serum samples + 5 x standard deviations = 0.19. Solid line represents cutoff value. The result was considered positive if a sample yielded OD_{450} above the cutoff.

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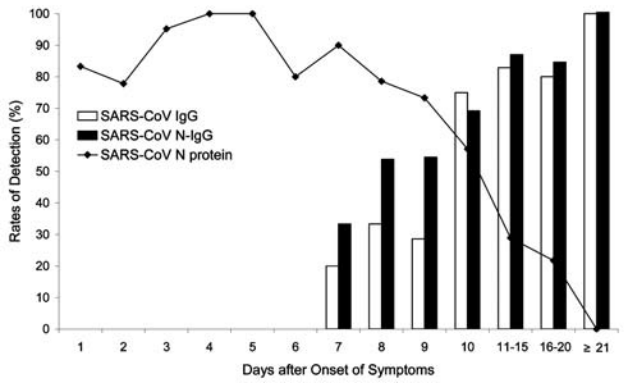

Figure 2. The profile of N protein detection in blood and antibody response to severe acute respiratory syndrome-associated coronavirus (SARS-CoV) from onset of symptoms to the convalescent phase. IgG, immunoglobulin G.

never detected beyond day 21. Using the same panel of the patient serum samples, we measured the N protein–specific IgG (SARS-CoV N-IgG) and SARS-CoV–specific IgG (SARS-CoV IgG) in serum samples by indirect ELISA, which progressively increased from day 7 onward (Figure 2). With the appearance of antibodies, the N protein detection rate decreased from day 10 after the onset of symptoms. However, from day 7 to day 18, a high level of N protein was still detectable in the serum samples from 11 patients with a mean of OD values of 1.65 when the SARS-CoV N-IgG had already increased to a level with a mean OD value of 1.18.

Serum samples from patients collected 4 years previously were used as negative controls. Patients thought to have cases of SARS on admission and later found to be uninfected by serologic testing, and healthcare workers who had close contact with SARS patients were tested for circulating N protein. Of the serum samples from non-SARS patients collected 4 years previously (n = 400), only one was weakly positive for N protein (OD = 0.288). We tested a total of 110 acute-phase serum samples from 105 patients, initially considered to have suspected SARS and later proven to be negative for SARS-CoV by serologic testing of convalescent-phase serum samples taken >28 days after onset of symptoms, and 315 serum samples from healthcare workers. All were negative for the N protein by capture ELISA. This finding resulted in a test specificity of 99.9% (1 of 825).

Conclusions

Our results suggest that N protein in the serum samples of SARS patients can be detected as early as day 1 after disease onset. Although the level of circulating N protein was highly variable from one person to another from day 1 to day 18, development of SARS-CoV N-IgG appears not to be affected by N protein during the acute phase of the infection, 7 days after the onset of symptoms. The positive detection rate of N protein in serum samples within the first 10 days of infection is higher than that detected by RT-PCR (8,9). Furthermore, the variation in the reported sensitivity and specificity of RT-PCR may be related to the lack of standardization of the assay and the specimen collection (6). Therefore, this viral antigen-capture ELISA may have greater sensitivity, specificity, and ease and reliability of in-use performance than the nucleic acid amplification assay. Further comparative studies with nucleic acid amplification tests should be undertaken at clinical laboratories serving acute-care hospitals where rapid SARS diagnosis is vital.

Acknowledgments

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Human Infection Caused by *Clostridium hathewayi*

Sameer Elsayed*† and Kunyan Zhang*†

We describe a 27-year-old man with acute cholecystitis, hepatic abscess, and bacteremia caused by *Clostridium hathewayi*, a newly described gram-negative, endospore-forming, rod-shaped bacterium. This report is the first of human infection caused by this microorganism.

The genus *Clostridium* is a phylogenetically heterogeneous group of anaerobic, endospore-forming, rod-shaped bacteria; they are usually gram positive, but some species may stain gram variable or gram negative (1,2). *Clostridium* strains are widely distributed in the environment and form part of the normal colonic microflora of humans and many animals (1,2). More than 150 species have been described to date, but most are believed to be harmless saprophytes (1). Pathogenic *Clostridium* spp. may be involved in a wide variety of human infections or illnesses. Such conditions are usually endogenous (e.g., brain abscess, pneumonia, intrabdominal abscess, cholecystitis, bacteremia) and arise from the host's own microflora; other illnesses may be exogenous (e.g., food poisoning, pseudomembranous colitis, tetanus, botulism, myonecrosis) (1). The most commonly encountered, clinically important clostridia include *Clostridium perfringens*, *C. clostridioforme*, *C. ramosum*, *C. butyricum*, *C. innocuum*, *C. septicum*, *C. tertium*, and *C. difficile* (1). *C. hathewayi* is a newly described species that was first reported by Steer et al. (3). The species was named after Charles L. Hatheway in recognition of his contributions to the *C. botulinum* group of organisms (3).

Case Report

Our patient was a 27-year-old, previously healthy Chinese man who immigrated to Canada 10 years previously. The patient sought treatment at the hospital for a 2-week history of intermittent fever and chills that were associated with sharp, nonradiating, right upper quadrant abdominal pain. He did not report nausea, vomiting, diarrhea, or jaundice. The patient did not use alcohol heavily, use intravenous drugs, or engage in high-risk sexual activity. The patient did not have a history of recent travel outside of Canada and was not taking any medications. His medical history and family history were unremarkable. Upon physical examination, the patient appeared mildly ill and had a temperature of 39.8°C, along with sinus tachycardia. Other findings were unremarkable except for mild right upper quadrant abdominal discomfort with deep palpation. Laboratory testing showed a peripheral leukocytosis with a left shift. Abdominal ultrasound and computed tomographic (CT) scans showed gallbladder wall thickening and inflammation, multiple gallstones, and a single large fluid collection in the right lobe of the liver, with multiple adjacent smaller satellite fluid collections. Acute cholecystitis and hepatic abscess were diagnosed. Two sets of BacT/Alert FAN (bioMerieux Inc., Durham, NC) aerobic and anaerobic blood cultures were drawn, after which the patient received empiric intravenous piperacillin-tazobactam therapy.

A large liver abscess was drained by using CT scans as a guide; samples of the liver abscess were submitted for aerobic and anaerobic culture. Gram stain of abscess fluid showed heavy neutrophils and gram-negative rods. After 48 hours of incubation in the BacT/Alert 3D system (bioMerieux, Inc.), the anaerobic bottles from both sets of blood cultures were positive for similar, gram-negative, rod-shaped bacteria. The blood and abscess isolates did not grow aerobically, although anaerobic growth on brucella blood agar media (PML Microbiologicals, Wilsonville, OR) showed identical-looking, nonhemolytic, motile organisms, with colonial and microscopic morphologic features typical of *Clostridium* spp. However, endospores were not visualized initially, and the organisms persistently stained gram negative. Growth was observed on anaerobic phenylethyl alcohol agar; attempts to grow the organisms on kanamycin-vancomycin laked blood and bacteroides bile esculin agars (PML Microbiologicals) failed. Both isolates demonstrated sensitivity to vancomycin (5 μg) and kanamycin (1,000 μg) and resistance to colistin (10 μg) special-potency identification discs. Tests for catalase, indole, lecithinase, lipase, and reverse Christie-Atkins-Munch-Peterson were negative. Since routine conventional phenotypic identification algorithms were not successful in identifying organisms, the isolates initially underwent partial 16S ribosomal RNA (rRNA) gene sequencing using MicroSeq 500 kits and an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Full-length sequencing of the 16S rRNA gene was subsequently performed for more definitive identification. The blood and abscess isolates had identical sequences; a GenBank BLAST (http://www.ncbi.nlm.nih.gov/BLAST/) search showed a 99% match of their full-length 16S rRNA gene profiles with those of a previously characterized strain of *C. hathewayi* (GenBank accession no. AJ311620). Repeat subculture and Gram

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stain of the organism showed the presence of gram-negative rods with subterminal endospores (Figure 1).

The isolates were susceptible to penicillin G (MIC = 0.064 μg/mL), clindamycin (MIC = 0.064 μg/mL), and metronidazole (MIC = 0.032 μg/mL) by Etest. Despite intense efforts, no other microorganisms were isolated from the blood or liver abscess specimens. Antimicrobial therapy was subsequently switched to intravenous ceftriaxone and metronidazole. After marked clinical improvement, the patient was discharged home on oral therapy.

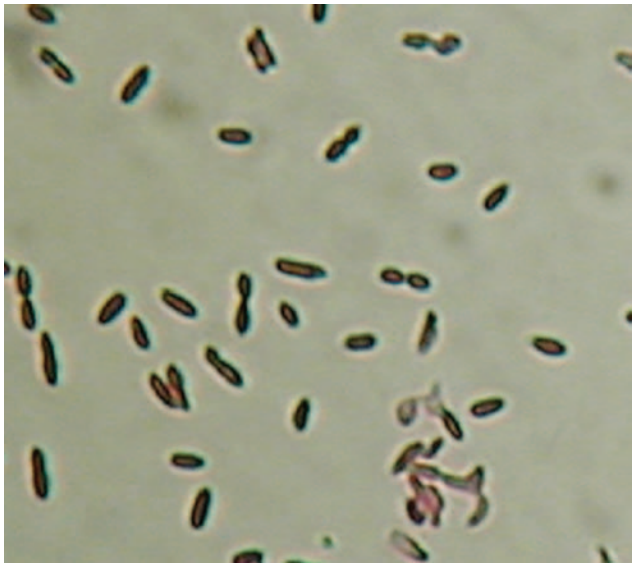

Figure 1. Gram strain of *Clostridium hathewayi* from growth on solid agar media. Note the gram-negative staining characteristics and presence of subterminal endospores. Magnification 1,000x.

Conclusions

Similar to certain members of the genus *Clostridium* (e.g., *C. clostridioforme* and *C. ramosum*), the organism has a propensity to stain gram negative (3). Subterminal, oval-to-round endospores may be visible. Strains may or may not be motile. Colonies are usually 3 mm in diameter after 72 hours of incubation and are nonhemolytic, grayish-white, opaque, convex, round, shiny, and have a slightly irregular margin (3), similar to our observations (Figure 2). Isolates are typically saccharolytic and ferment a variety of carbohydrate compounds but fail to hydrolyze gelatin or urea, reduce nitrate, or produce indole, lecithinase, or lipase (3). Although these phenotypic tests can possibly distinguish this organism from closely related species, these methods are too cumbersome and time-consuming for routine use in the clinical setting. However, the increasing ease, availability, and affordability of identification methods that use DNA sequencing have identified uncommon microbial pathogens that are difficult to identify and often encountered in the clinical microbiology laboratory. The 16S rRNA gene (≈1,500 bp in size) is ubiquitous in all eubacteria and has served as the principal target of bacterial identification protocols that are sequence-based. Each unique bacterial species has a distinctive 16S rRNA gene sequence profile (signature); hence, the signatures of unknown bacteria can then be compared to publicly available or commercial sequence databases to determine if the organism belongs to a particular known species.

Although the sequence profile of our isolate (GenBank accession no. AY552788) was 99% identical to the type strain of *C. hathewayi* reported by Steer et al. (3) (GenBank accession no. AJ311620), the two sequences are believed to be completely identical since the 1% difference in the sequence profiles was attributed to uncharacterized bases in the sequence reported by Steer. *C. hathewayi* displays the closest phylogenetic relationships with *C. celerecresens* and *C. sphenoides* (Figure 3), which may be found as part of the normal human colonic microflora (3,4). However, the natural habitat of *C. hathewayi* is not known. To the best of our knowledge, human infection caused by this bacterium has not been previously reported.

The two isolates described by Steer et al. (3) were recovered from a phytic acid-degrading, organism enriching chemostat that had been injected with human feces from healthy donors. In contrast, the isolation of *C. hathewayi* from our patient's blood and hepatic abscess fluid specimens is convincing evidence of its clinical importance, although this finding needs to be corroborated by animal studies. The finding is not surprising, given that *Clostridium* spp. are not uncommonly implicated in cases of acute cholecystitis and associated bacteremia (5). Our

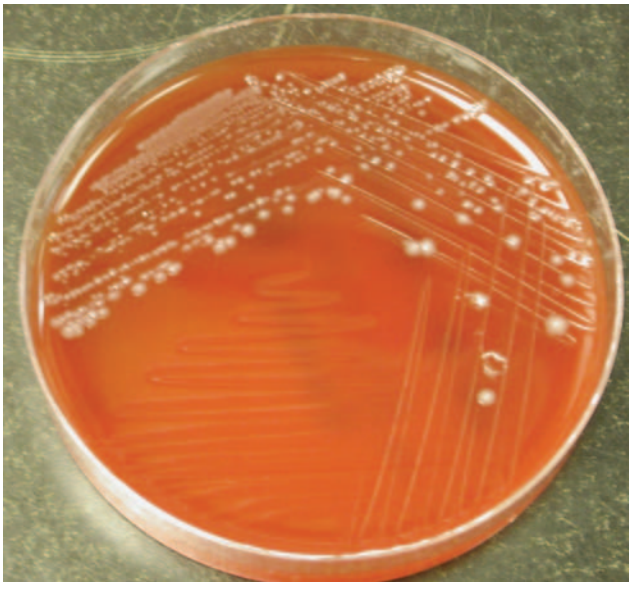

Figure 2. Colonial morphology of *Clostridium hathewayi* on brucella blood agar media after 48 hours of anaerobic incubation.

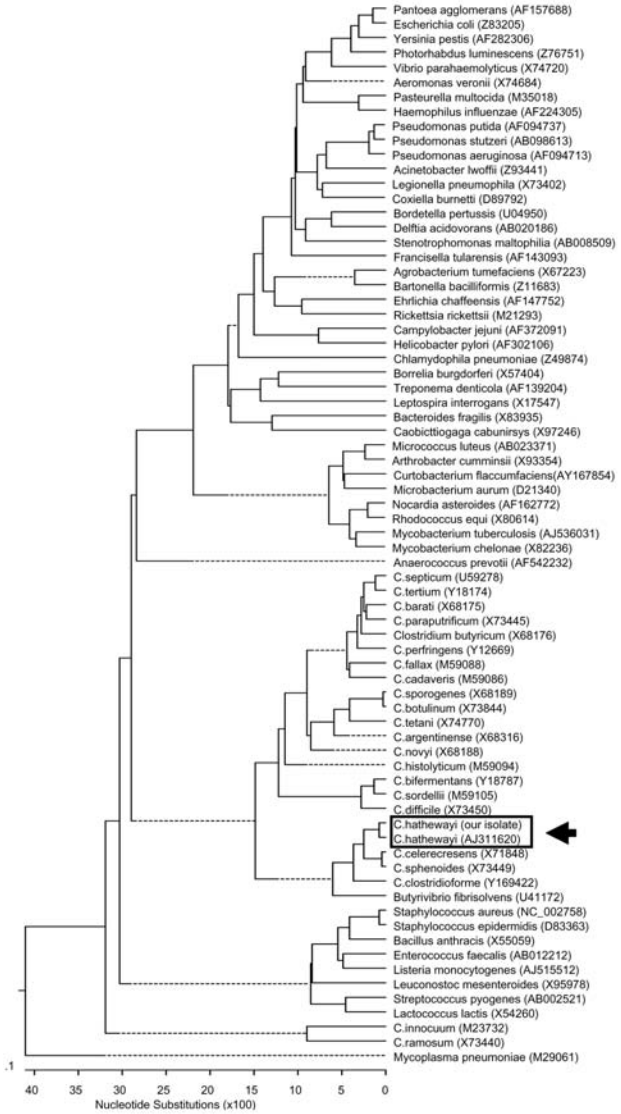

Figure 3. Phylogenetic tree showing the 16S rRNA relationships of our *Clostridium hathewayi* isolate (GenBank accession no. AY552788) wth various *Clostridium* species and other medically important bacteria. The tree was constructed by Clustal W analysis (DNASTAR Inc., Madison, WI), based on the entire 16S rRNA gene. The sequences were obtained from the GenBank database with their nucleotide sequence accession numbers in brackets. *Mycoplasma pneumoniae* was used as the outgroup to root the tree. Our *C. hathewayi* isolate and the published *C. hathewayi* strain (GenBank accession no. AJ311620) are boxed and delineated with an arrow.

report highlights the importance of *C. hathewayi* as a potential human pathogen.

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Commercial Logging and HIV Epidemic, Rural Equatorial Africa

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We found a high seroprevalence of HIV among young women in a commercial logging area in Cameroon. The vulnerability of these young women could be related to commercial logging and the social and economic networks it induces. The environmental changes related to this industry in Equatorial Africa may facilitate HIV dissemination.

More than 20 years after the beginning of the HIV epidemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) stated that the epidemic was now taking hold in many African countries (1). An estimated 25.0–28.2 million persons are already infected in sub-Saharan Africa, accounting for 70% of all infections worldwide, and Africans represent 10% of the world population. AIDS is now the leading cause of death in Africa (2.2–2.4 million deaths in 2003) (2). UNAIDS particularly underlined the rapidly rising prevalence in Cameroon, a central African country (4.7% in 1996, 11.8% in 2001) (1,3). As in many countries, these data come from sentinel surveillance of women attending urban and semi-urban antenatal clinics.

Data from rural areas are scarce, and the dynamics of HIV infection are poorly documented. Travel has been linked to an increased risk among rural populations (4). The recent environmental changes related to commercial logging in Equatorial Africa could potentially facilitate HIV dissemination. Commercial logging has led to road construction in remote forested areas, human migration (especially of single men), and develop social and economic networks (including commercial sex work) that support this industry (5). In Cameroon, commercial logging has been growing for at least 4 decades. We have previously shown that these environmental changes might represent a risk to human health through exposure to simian immunodeficiency viruses (6). We investigated the seroprevalence of HIV, the nature of circulating HIV genetic variants, and factors associated with HIV infection in a logging area of southern Cameroon.

The Study

A cross-sectional, community-based survey was performed in September 2001 in a remote village where a sawmill and logging camp have been located since 1973 (Nkonzuh, East Province) and also in two neighboring villages (Mboumo and Kompia, 10 km and 30 km from the logging camp, respectively). The three villages are 250 km east of Yaoundé, the capital of Cameroon (Figure). The total population of the three villages has increased since commercial logging began and was estimated at 1,000 inhabitants at the time of the survey (excluding the logging camp). Approximately 200 workers are employed in this industry; approximately half originate from the region. Some workers live in the traditional neighborhoods of Nkonzuh, and a small number live in Mboumo and Kompia; most live in the logging camp. The survey in Nkonzuh was carried out in the traditional neighborhoods but not in the logging camp itself. All inhabitants >15 years of age were asked to participate in the survey during door-to-door visits. After participants gave informed consent, they were interviewed by using a verbal standard questionnaire in French or a local language. The data gathered included the village name, time spent in the village, house number, date of birth or age, sex, ethnic group, marital status, level of education, occupation, and history of blood transfusion, injection, surgery, circumcision or excision, tattoo, and sexually transmitted infections (STI).

Serologic screening for HIV infection was based on an enzyme-linked immunosorbent assay (ELISA) (Murex HIV-1.2.O, Abbott, Rungis, France). All positive samples were confirmed and typed (HIV-1 or -2) by using a line immunoassay (INNO-LIA HIV-1+2, Innogenetics, Ghent,

Figure. Detail of map of Cameroon, with study area indicated.

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Belgium). All positive samples were further typed (HIV-1 group M, N, O or HIV-2) with an in-house ELISA based on V3 loop peptides. HIV-1–positive samples were genetically characterized in the *gag* and *env* genes by sequencing and phylogenetic analysis, as described (7). Syphilis was diagnosed by using the rapid plasma reagin (RPR) (Becton Dickinson, Mountain View, CA) and *Treponema pallidum* hemagglutination (TPHA) (Sanofi Pasteur, Chaska, MN) tests.

The χ^2 and Fisher exact tests were used to compare the distribution of categorical variables between men and women. For continuous variables, comparisons were based on the nonparametric Mann-Whitney two-sample test. Multivariate random-effects logistic regressions, including sex-specific analyses, were used to identify factors associated with HIV infection (8). Independent variables associated with HIV infection, identified by using a conservative threshold of $p < 0.25$ in univariate analysis, were retained for multivariate analysis. Ninety-five percent confidence intervals (CI) of proportions were estimated by using the binomial exact method.

Four hundred eighty-four persons were enrolled (Table 1). Most (77.8%) were Badjoe, a local ethnic group, and 6.4% were Pygmies; 25 other ethnic groups were also

Table 1. Characteristics of the study population and category-specific HIV seroprevalence in a commercial logging area, southern Cameroon, 2001[a]

	Men (N = 228)				Women (N = 256)			
Characteristic	n	HIV+ (%)	OR	95% CI	n	HIV+ (%)	OR	95% CI
Village of residence								
Nkonzuh	66	6.3	1.00		84	14.5	1.00	
Mboumo	70	4.4	0.68	0.15–3.17	75	6.9	0.44	0.15–1.32
Kompia	92	0.0	–		97	11.3	0.77	0.32–1.86
Median time spent in the village (y)	23				15.2			
Ethnic group								
Badjoe	184	2.7	1.00		190	11.2	1.00	
Pygmies	18	0.0	–		13	0.0	–	
Others	25	8.3	3.18	0.58–17.39	51	14.0	1.28	0.51–3.21
Age group (y)								
15–24	73	1.4	0.89	0.05–14.46	71	10.0	2.11	0.59–7.54
25–34	51	6.0	3.96	0.40–39.26	51	22.5	5.65	1.68–18.94
35–49	39	5.1	3.54	0.31–40.48	52	11.5	2.48	0.66–9.25
≥50	65	1.6	1.00		82	4.9	1.00	
Marital status								
Married	124	3.3	1.00		139	4.4	1.00	
Free union	16	6.3	1.95	0.20–18.62	22	36.4	12.19	3.70–40.22
Single	64	1.6	0.48	0.05–4.38	38	18.4	4.82	1.51–15.35
Divorced	8	12.5	4.88	0.47–50.60	8	25.0	7.11	1.18–42.91
Separated	4	0.0	–		11	18.2	4.74	0.83–26.93
Widowed	10	0.0	–		37	8.1	1.94	0.46–8.17
Level of education								
Never schooled	22	0.0	–		68	2.9	1.00	
Primary school	152	2.0	1.00		156	12.4	4.64	1.05–20.54
Secondary school or higher	54	7.7	4.17	0.90–19.31	32	22.6	9.48	1.84–48.85
Occupation								
None	2	0.0	–		21	5.0	1.00	
Culture	126	2.4	1.00		206	11.8	2.56	0.33–20.01
Hunting	29	3.7	1.56	0.03–20.31	0	–	–	
Retired	6	0.0	–		1	0.0	–	
Other	57	5.5	2.44	0.31–18.74	25	12.5	2.71	0.26–28.37
Potential risk factors for HIV infection								
Blood transfusion	2	0.0	–		10	33.3	4.32	1.02-18.35
Injection	220	3.2	–		248	11.0	0.75	0.09–6.47
Surgery	31	3.2	1.02	0.02–8.89	39	5.3	0.40	0.09–1.75
Circumcision	220	3.2	–		–	–		
Excision	–				0	–		
Tattoo	10	10.0	3.80	0.41–34.94	28	17.9	1.88	0.65–5.42
Sexually transmitted infection	90	5.6	3.87	0.73–20.40	37	21.6	2.66	1.07–6.60
Serologic evidence of syphilis[b]	19	5.3	1.93	0.22–16.99	27	7.4	0.61	0.14–2.71

[a]+, positive; OR, odds ratio; CI, confidence interval.
[b]Rapid plasma reagin and *Treponema pallidum* hemagglutination positive.

represented. The HIV serologic results were available for 476 persons. Seven persons refused venipuncture after interview, and one sample could not be analyzed. These eight persons did not differ from the other persons in term of sex (50.0% women vs. 47.1% women) but were slightly younger (median, 26.8 years vs. 34.9 years). Five (1.1%) of the 476 HIV serologic results were indeterminate, and these persons were excluded from the analysis of risk factors. The overall HIV seroprevalence was 7.4% (CI 5.2%–10.1%). Women had a far higher HIV seroprevalence than men (overall 11.1% vs. 3.1%) (Table 2), which ranged from 4.9% in women at least 50 years of age to 22.5% in the 25- to 34-year age group. In men, the HIV seroprevalence ranged from 1.4% in the 15- to 24-year age group to 6.0% in the 25- to 34-year age group. The HIV seroprevalence was higher for both sexes, although not significantly, in the village in which the logging camp is located than in the two surrounding villages (Table 1).

All 35 seropositive persons were infected by HIV-1, and no one was coinfected by HIV-2. Samples from 28 persons reacted with group M peptides, and two others reacted with both group M and O peptides. Five serum samples did not react with group M, N, or O peptides. Twenty-six of the 35 seropositive samples could be amplified, and all were genetically characterized, in both *gag* and *env* (n = 24), *gag* only (n = 1), or *env* only (n = 1). The circulating recombinant form (CRF) 02_AG strain predominated (72.0% in *gag* and 76.0% in *env*), and several other variants cocirculated (subtypes A, F2, G, and H and CRF06_cpx and CRF11_cpx). A discordant profile was observed between the *gag* and *env* genes in three persons (12.5%): A^{gag}/H^{env}, $G^{gag}/CRF06\_cpx^{env}$, $G^{gag}/CRF11\_cpx^{env}$, respectively.

In univariate analysis, HIV infection in women was associated with age group ($p = 0.03$), marital status ($p = 0.002$), level of education ($p = 0.03$), history of blood transfusion ($p = 0.05$), and STI ($p = 0.04$) (Table 1). In men, no factors were associated with HIV infection. In multivariate analysis, HIV infection remained strongly associated with sex (odds ratio 10.22; CI 3.19–32.80; $p < 0.001$), after adjustment for marital status, level of education, and history of STI. No specific risk factors were found in men. In contrast, women who are unmarried, educated, or have a history of an STI were more likely to be infected by HIV than women who were married, never-schooled, or did not have a history of an STI (Table 3).

Conclusions

We identified a population with a high seroprevalence of HIV infection; nearly one quarter of women 25–34 years of age were infected. The HIV seroprevalence among women 15–44 years of age (median 26 years) was slightly higher than among women of the same age group (median 22 years) who attended urban and semiurban antenatal clinics in the East Province (14.5% vs. 10.0%) (9). HIV seroprevalence among women was comparable in the 15- to 24-year age groups (10.0% vs. 10.4%) and the 35- to 44-year age groups (11.5% vs. 12.5%), while it was much higher in the 25- to 34-year age group (22.5% vs. 8.3%). Lower seroprevalence rates among women who went to the antenatal clinics than in the general female population have been reported in several African countries, which is attributable to lower fertility among HIV-infected women (10), but the far higher rate observed in our 25- to 34-year age group is particularly striking.

The overall HIV seroprevalence was higher, although not significantly, in our survey (7.4%, CI 5.2%–10.1%) than in another survey conducted in villages of the same province (4.5%, CI 3.3%–6.1%) (11). The villages we surveyed are more readily accessible by car, which favors travels to and from places with higher HIV seroprevalence (towns and other regions). The proportion of Pygmies, who are known to have a low HIV seroprevalence (12), confirmed by our results, is lower in the area we surveyed. Some villages surveyed by Nyambi et al. (11) were located in an area with a more recent history of logging activity where environmental changes had not yet fully affected the epidemic.

The high HIV seroprevalence in women 25–34 years of age living in this rural area could be related to commercial logging. In a context in which workers had relatively high salaries (U.S. $60 to U.S. $530 per month), sexual networks were extensive and complex (13). An estimated 40 female sex workers were permanently living in the logging camp (S. Loul, pers. comm.). In addition, ≈100 women arrived at the logging camp from towns or neighboring vil-

Table 2. Seroprevalence of HIV infection according to sex and age in a commercial logging area, southern Cameroon, 2001[a]

	Men			Women			Both	
Age groups (y)	No. tested	HIV+ (%)	95% CI	No. tested	HIV+ (%)	95% CI	OR[b]	95% CI
15–24	71	1.4	0.1–7.6	70	10.0	4.1–19.5	7.78	0.93–64.98
25–34	50	6.0	1.3–16.6	49	22.5	11.8–36.6	11.38	0.79–163.10
35–49	39	5.1	0.6–17.3	52	11.5	4.4–23.4	3.25	0.30–35.41
≥50	64	1.6	0.1–8.4	81	4.9	1.4–12.2	3.26	0.36–29.95
Total	224	3.1	1.3–6.3	252	11.1	7.5–15.7	4.39	1.74–11.08

[a]CI, confidence interval; OR, odds ratio.
[b]HIV prevalence in women versus men.

Table 3. Multivariate analysis of factors associated with HIV infection among women living in a commercial logging area, southern Cameroon, 2001[a]

Variable	Adjusted OR[b]	95% CI[b]
Marital status		
Married	1.00	
Free union	10.85	3.10–37.92
Single	4.33	1.31–14.33
Divorced	10.78	1.55–75.09
Separated	3.73	0.59–23.41
Widowed	5.91	1.01–34.44
Level of education		
Never schooled	1.00	
Primary school	6.04	0.97–37.49
Secondary school	10.17	1.27–81.45
History of STI		
No	1.00	
Yes	3.14	1.12–8.81

[a]OR, odds ratio; CI, confidence interval.
[b]Initial model included village of residence, time spent in the village, age group, marital status, level of education, and history of blood transfusion, surgery, tattoo and sexually transmitted infection (STI). ORs compare each category individually to the first category.

lages at the time of salary distribution (twice a month), to trade or offer paid sex (U.S. $1.50 per intercourse). Some men and women had sex with several partners a night. Some workers' wives also had extramarital sex. Seroprevalence in both sex and odds ratio when men and women are compared are age-specific; seroprevalence in women 25–34 years of age is greater for those in our study than those in the sentinel surveillance. The lack of association with local risk factors, such as blood transfusion and injection, and the results of the multivariate analysis suggest that young, unmarried, and educated local women could be mainly infected by workers during unprotected relationships in exchange for money or goods. The high prevalence of syphilis confirmed high-risk sexual behavior (11.8% in women 15–44 years of age compared to 3.6% among those who attended antenatal clinics) (9).

HIV-1 genetic diversity and its distribution were similar to that observed in towns (7,14), which suggests that the spread of HIV in this rural area results from numerous introductions of the virus. The vulnerability of this rural population, especially young women, to HIV infection could be related to commercial logging and the social and economic networks it creates.

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Burkholderia cenocepacia Vaginal Infection in Patient with Smoldering Myeloma and Chronic Hepatitis C

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We report a case of a vaginal infection caused by a strain of *Burkholderia cenocepacia*. The strain was isolated from vaginal swab specimens from a 68-year-old woman with smoldering myeloma and chronic hepatitis C virus infection who was hospitalized for abdominal abscess. Treatment with piperacillin/tazobactam eliminated *B. cenocepacia* infection and vaginal symptoms.

Members of genus *Burkholderia* are aerobic, non–spore-forming, catalase-positive, gram-negative bacteria; most are oxidase positive (1). This genus comprises opportunistic pathogens responsible for important infections in immunocompromised persons and in cystic fibrosis (CF) patients (2,3). To date, the genus *Burkholderia* comprises more than 30 species, including the *Burkholderia cepacia* complex, *B. mallei*, and *B. pseudomallei* (2). The *B. cepacia* complex is a group of microorganisms composed of at least nine closely related genomovars (2,3). All genomovars have been shown to cause infections, and *B. cenocepacia* and *B. multivorans* (genomovars III and II, respectively) are the genomovars most frequently isolated from CF patients (4–7).

Nosocomial infections caused by *B. cepacia* complex have been reported in non-CF patients, principally associated with the use of contaminated disinfectants, anaesthetic solutions, and invasive treatments such as urinary and intravenous catheterization (8). These strains are intrinsically resistant to most antimicrobial agents and are difficult to eliminate (8,9). Cases of *B. cepacia* complex infections are underestimated because of the complex taxonomy of this genus and the poor sensitivity and specificity of commercial identification systems (10). Recently, molecular methods, mainly polymerase chain reaction (PCR)-based, have been developed to circumvent this issue (10–13).

We report a case of vaginal infection, caused by *B. cenocepacia,* in a patient affected by smoldering myeloma, and chronic hepatitis C virus (HCV) infection. Bacterial identification at species level was assessed by four combined PCR–based molecular methods. Therapy based on treatment with piperacillin/tazobactam completely eliminated the infection as well as the vaginal symptoms.

Case Report

In August 2003, a 68-year-old woman with smoldering myeloma and chronic HCV infection (the patient had cirrhosis since 1994) was admitted to the "Sant'Andrea" Hospital (2nd Faculty of Medicine, "La Sapienza" University, Rome, Italy), with a 15-day history of fever, malaise, asthenia, fatigue, abdominal pain, and swelling of lower limbs. One week before admission, she had been treated with ciprofloxacin (500 mg twice a day) without improvement of any of the clinical symptoms. On admission (day 1), the patient had a fever (38.4°C) and showed abundant ascitic fluid and jaundice. Laboratory values were indicative of macrocytic anemia (erythrocytes, 3.6 x 10^9/L; hemoglobin, 110 g/L; mean corpuscular volume, 103 fL; hematocrit, 31%; serum iron level, 10.74 μmol/L; and serum ferritin level, 170 μg/L. Platelet count was 46 x 10^9/L, and leukocyte count was 14 x 10^9/L with neutrophils (13 x 10^9/L) and lymphocytes (0.5 x 10^9/L). The patient had high values of the erythrocyte sedimentation rate (ESR) in the first hour (71 mm/h) and C-reactive protein (CRP) (4.1 mg/L). Increased total serum proteins (8.1 g/dL) and hypoalbuminemia (23 g/L) were also detected. Six blood samples were taken at 3-hour intervals during the first day of hospitalization and cultured to detect the growth of aerobic and anaerobic microorganisms (Bactec System, Becton Dickinson, Sparks, MD). All blood cultures were negative. Abdominal ecographic and tomographic scans showed a pseudocystic formation in the pancreas. The pancreatic formation was drained because surgical intervention was not appropriate for the patient. On admission day 2, the patient was transferred to the Infectious Diseases Unit; there, intensive strong diuretic therapy was initiated, and a urinary catheter was inserted. Results of microbiologic analysis of urine and of a liquid taken from the pseudocystic formation were negative for common pathogenic bacteria. In spite of these results, the patient was given intravenous amoxicillin/clavulananate (1.2 g three times a day) and amikacin (1 g once a day) (day 3). After 5 days of antimicrobial drug therapy, the

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clinical symptoms of the patient slightly improved. On day 9 (i.e., after 6 days of antimicrobial drug therapy and 7 days of urinary catheterization), the patient exhibited an abundant white vaginal discharge with vulvar pain and burning. Vaginal swabs were streaked on different selective media. Columbia agar base, supplemented with 5% (vol/vol) sheep blood, and MacConkey agar plates showed a monomicrobic culture constituted by catalase-positive and oxidase-positive gram-negative rods that did not grow under anaerobic conditions. A presumptive identification of *B. cepacia* was made by using the API20NE (bioMérieux, Marcy l'Etoile, France), while the Vitek 2.0 identification system (bioMérieux) did not recognize the isolate as *B. cepacia* (10). Identification at the species level was achieved by four different PCR-based combined molecular methods, namely, *Dde*I and *Hae*III restriction fragment length polymorphisms (RFLP) of 16S rDNA and *recA* gene analysis, *recA* genomovar-specific PCR, and *recA* sequence analysis (11–13). Control strains belonging to different genomovars of *B. cepacia* complex were included in all molecular analyses (14). Bacterial genomic DNA was extracted by using a commercial kit (Qiagen genomic-tip, Qiagen Inc., Hilden, Germany) as previously described (14). The bacterial isolate showed a 16S rRNA *Dde*I-RFLP pattern 1 and a *recA Hae*III-RFLP pattern H (data not shown; 14), patterns indicative of *B. cenocepacia* (11–14). Genomovar-specific PCR was performed with primer pairs annealing to internal regions of the *recA* gene (12,13). A DNA fragment with a molecular mass of approximately 800 bp, consistent with the expected 781-bp *B. cenocepacia* amplification fragment, was successfully amplified with the primer pair BCRG3B1/BCRG3B2 (data not shown) (12,13). To unambiguously identify the bacterial isolate, we sequenced the amplified *recA* DNA fragment that was subjected to *recA Hae*III-RFLP analysis (13). The *recA* DNA sequence of the bacterial isolate (GenBank accession no. AJ786367), subjected to BLAST analysis (http://www.ncbi.nlm.nih.gov/BLAST), showed >99% homology with the *recA* sequence of the *B. cenocepacia* reference strain LMG 18829 (GenBank accession no. AF143784). Phylogenetic analysis, based on *recA* DNA sequences, indicated that the clinical isolate belonged to the *B. cenocepacia* (genomovar III, lineage IIIB) (Figure) (4,13).

The *B. cenocepacia* isolate was resistant to penicillin, mezlocillin, piperacillin, amoxicillin/clavulanate, nitrofurantoin, ciprofloxacin, carbapenems, cephalosporins, aminoglycosides, and tetracycline and sensitive to trimethoprim/sulfamethoxazole and piperacillin/tazobactam. When the antimicrobial drug susceptibility profile was considered, the amoxicillin/clavulanate and amikacin antibiotic therapy was interrupted, and intravenous piperacillin/tazobactam combination was administered

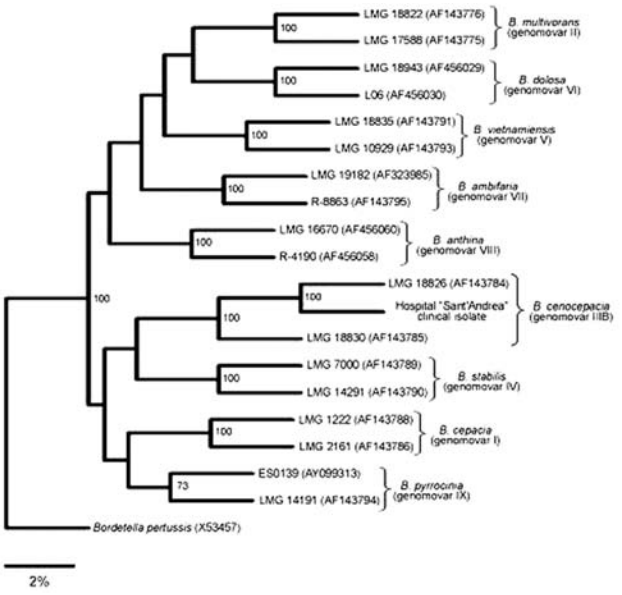

Figure. The consensus phylogenetic tree of *recA* DNA sequences of *Burkholderia cepacia* complex strains, representative of each genomovar, and of the *B. cenocepacia* isolate (GenBank accession no. AJ786367) was constructed with the PHYLIP package (version 3.6) (http://evolution.genetics.washington.edu/phylip.html). Only *recA* DNA sequences of reference *B. cenocepacia* strains (genomovar III, lineage IIIB) are included in the tree (4,13). Alignments were performed with the Clustal W program. Genetic distance is indicated on the scale

(4.5 g, three times a day for 4 weeks). Vaginal swabs were taken every 3 days during the 4 weeks of the antimicrobial drug therapy and, afterwards, every 20 days for a total follow-up period of 3 months. After 10 days of the piperacillin/tazobactam treatment, vaginal symptoms disappeared and cultured vaginal swabs did not show *B. cenocepacia*. After the piperacillin/tazobactam treatment ended, the patient did not exhibit any signs of vaginal infection.

Conclusions

We think this is the first description of a vaginal infection caused by *B. cenocepacia*. The patient's immunodepression from smoldering myeloma and chronic HCV likely favored vaginal colonization by *B. cenocepacia*. Urinary catheterization might have favored vaginal colonization by *B. cenocepacia*, even if we did not isolate *B. cenocepacia* from catheters, disinfectants, and selected hospital environmental samples analyzed from October 2003 to date February 2004 (15). Moreover, the antimicrobial agents, ciprofloxacin, and amoxicillin/clavulanate and amikacin, administered to the patient before and during hospitalization, might also have altered the patient's vaginal flora. Piperacillin/tazobactam eliminated vaginal symptoms and *B. cenocepacia* from the vaginal mucosa,

thus indicating that the detected isolate was indeed responsible for the infection.

Microorganisms belonging to the *B. cepacia* complex are difficult to identify by conventional biochemical tests and commercial systems (8). This case report highlights the importance of the use of molecular techniques to quickly and accurately identify members of the *B. cepacia* complex (10,13). The ability of *B. cenocepacia* to cause vaginal infections is unusual. Further studies are needed to clarify whether specific virulence factors are carried and expressed by the *B. cenocepacia* clinical isolate, conferring to this strain the specific ability to colonize and multiply within the vaginal mucosa.

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Decreased Levofloxacin Susceptibility in *Haemophilus influenzae* in Children, Hong Kong

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Among 563 strains of *Haemophilus influenzae* from young children in Hong Kong, 5 (0.9%) had decreased susceptibility to quinolones. The five strains had a Ser-84-Lys or Asp-88-Asn substitution in GyrA. Pulsed-field gel electrophoresis showed that the isolates are genetically diverse.

Although fluoroquinolone-resistant *Haemophilus influenzae* were reported a decade ago (1), this resistance phenotype has remained rare (2). In general, resistance to fluoroquinolone is chromosome-mediated, involves mutations in one or both target genes encoding DNA gyrase and topoisomerase IV, and tends to develop in a stepwise manner. The MICs of various antimicrobial agents for such mutant strains increases with each additional mutation in the target sites. In *H. influenzae*, high-level resistance to the fluoroquinolones generally occurs in the presence of mutations involving both *gyrA* and *parC*. In *H. influenzae*, *gyrA* is the primary target for fluoroquinolones because *gyrA* mutations have generally arisen before *parC* mutations in resistant clinical isolates (2). First-step *gyrA* mutants showed reduced susceptibility to fluoroquinolones, but the MICs remain in the susceptible range. Resistance mechanisms in these isolates will be undetected if the fluoroquinolones' susceptibility was determined and the results interpreted according to the current breakpoints. We assessed the susceptibility of *H. influenzae* nasopharyngeal isolates, obtained from children throughout Hong Kong, to nalidixic acid and levofloxacin.

The Study

During the study period (December 1999 to June 2000), a total of 1,978 children, 2 to 6 years of age, were recruited from 79 daycare centers or kindergartens throughout Hong Kong. Details of the study population and the findings in relation to *Streptococcus pneumoniae* have been described (3). In brief, nasopharyngeal swab specimens were obtained from a predetermined number of children in each daycare center or kindergarten. On average, 25 children (standard deviation [SD] 11) from each institute were examined. For isolation of *H. influenzae*, a previously described selective medium (chocolate gonococcal [GC] agar base with sheep blood, supplemented with 1% yeast autolysate and vancomycin 5 μg/mL, bacitracin 300 μg/mL, and clindamycin 1 μg/mL) was used for swab inoculation (4). Plates to which samples were added were incubated in 5% CO_2 for ≤48 h. All isolates were identified by colony morphologic features, Gram stain, and requirement for both X and V factors.

The MICs of nalidixic acid, levofloxacin, ampicillin, and azithromycin were determined by the MIC microbroth dilution method with an in-house *Haemophilus* test medium broth (5) and interpreted according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines (6). Quality control strains (*H. influenzae* ATCC 49247 and ATCC 49766) were included with each run. All isolates were tested for the production of β-lactamase by nitrocephin paper disks (Cefinase, BBL, Becton Dickinson Microbiology Systems, Franklin Lakes, NJ).

The subset of isolates with reduced susceptibility to levofloxacin was examined further by pulsed-field gel electrophoresis (PFGE) using *Sma*I for DNA digestion (7), and the results were interpreted according to Tenover et al. (8). The isolates were also examined for *gyrA* and *parC* mutations by using primers and methods described (7).

The median age (interquartile range) for these 1,978 children was 5.3 years (4.3–5.3 years); the mean age was 5 years. Approximately half of the children were boys (52.7%). Sixty-three percent of surveyed children had siblings ≤12 years of age; 277 (14%) of the children had an overcrowded living environment (living space ≤5.5 m^2/person, according to the guideline of the Hong Kong Housing Authority). At the time of the survey, 103 (5.2%) of the 1,978 children were reported to be taking antimicrobial agents. In the 3 months before the study, 1,535 (77.6%) had visited their family doctor, and 63 (3.2%) had been hospitalized.

Overall, the carriage rate of *H. influenzae* was 28.5% (range 17%–42.1%). The MICs of nalidixic acid and levofloxacin for all isolates are shown in Table 1. Five (0.9%) isolates were resistant to nalidixic acid with MICs of 64 μg/mL to 128 μg/mL. The levofloxacin MICs of the same five isolates were 0.125 μg/mL, which is higher than the MICs (range 0.0019–0.06 μg/mL; mode 0.015) of the same antimicrobial drug for the nalidixic acid–sensitive isolates. Of the 563 isolates, 158 (28.1%) were β-lactamase–positive strains and thus were resistant to ampicillin.

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Table 1. Levofloxacin and nalidixic acid MIC distributions of all *Haemophilus influenzae* strains

MIC (μg/mL)	No. of strains	
	Levofloxacin	Nalidixic acid
0.001875	1	0
0.00375	1	0
0.0075	24	0
0.015	464	0
0.03	66	0
0.06	2	0
0.125	5	0
0.5	0	105
1	0	303
2	0	147
4	0	2
8	0	1
64	0	4
≥128	0	1

All isolates were susceptible to azithromycin with an MIC_{50} of 1 μg/mL and an MIC_{90} of 2 μg/mL.

None of the five children with nalidixic acid–resistant *H. influenzae* had been previously hospitalized. All five children had been treated with antimicrobial drugs in the previous 3 months, and two were taking antimicrobial drugs at the time samples were obtained. The specific antimicrobial agents were unknown. Two children had asthma, and the remaining three children had no underlying diseases.

The quinolone resistance–determining regions of *gyrA* and *parC* for the eight isolates with resistance or reduced susceptibility to nalidixic acid (MIC ≥ 4 μg/mL) or levofloxacin (MIC ≥0.06 μg/mL) were sequenced (Table 2). A Ser-84-Lys or Asp-88-Asn substitution was found in GyrA in all five isolates with resistance to nalidixic acid. No substitutions occurred in ParC. No amino acid substitution was found in either GyrA or ParC in the three isolates with reduced susceptibility to nalidixic acid (MIC 4–8 μg/mL). In pulsed-field gel electrophoresis analysis, the five nalidixic acid–resistant strains had distinct patterns and were unrelated.

Conclusions

Our data have shown, for the first time, resistance to quinolones among *H. influenzae* isolates in children. The finding is of clinical and public health concern, particularly in regions like Hong Kong where levels of antimicrobial resistance among respiratory pathogens are already high, and fluoroquinolone resistance in *S. pneumoniae* is emerging (9,10). The finding is also unexpected because fluoroquinolones are not approved for use among children in Hong Kong; such agents are not approved for children in the rest of the world as well. We believe that three potential explanations may account for the detection of fluoroquinolone resistance among children. First, nalidixic acid is approved to treat pediatric infections and is widely used in Hong Kong for outpatient and inpatient treatment of urinary tract infections and, occasionally, to treat shigellosis in children. In the Queen Mary Hospital, for instance, 13.5 and 10.0 defined daily doses per 100 pediatric admissions of nalidixic acid were used in 1999 and 2000, respectively (1 defined daily dose of nalidixic acid equals 4 g). In children, carriage of *H. influenzae* is common. The identified first-step mutant might be selected de novo when isolates colonizing the nasopharynx are exposed to the selection pressure from nalidixic acid. Second, use of fluoroquinolones in food animals is common in many Asian countries (2). Children could be exposed to residues of fluoroquinolones by consuming meat or dairy products from food animal previously fed antimicrobial agents from this group. At present, we do not know how exposure to residues of antimicrobial agents in food contributes to resistance (11). Presumably, the level of exposure from dietary source would be low. In the nasopharynx, the level of quinolone is approximately half the level it would be in the blood (12). If food levels of quinolones are controlled to within the acceptable minimum residual levels, the contribution from this route of potential exposure should be minimal. Finally, transmission from adults to children might have occurred in household settings. Although adult-to-child transmission appears to be uncommon,

Table 2. MIC and QRDR amino acid substitutions of *Haemophilus influenzae* ATCC 49247 and eight clinical isolates from young children

Isolate	School	Sex/Age (y)	MIC				Predicated QRDR amino acid changes	
			NA	LVX	AMP	AZI	GyrA	ParC
ATCC 49247	–	–	1	0.015	4	1	^{80}PHGDSAVYDTIVR^{92}	^{80}PHGDSACYEAMVL^{92}
G813	G8	M/6	4	0.03	1	2	None	None
G92	G9	M/4	4	0.06	0.25	1	None	None
D19	D1	M/6	8	0.06	0.25	1	None	None
L38	L3	F/5	64	0.125	0.5	1	D88N (gat to aat)	None
J517	J5	M/6	64	0.125	0.5	2	S84L (tcc to ttg)	None
M65	M6	F/6	64	0.125	128	1	S84L (ttc to tta)	None
B211	B2	F/4	64	0.125	0.25	1	S84L (tcc to tta)	None
R33	R3	F/5	128	0.125	0.25	1	S84L (ttc to tta)	None

[a]QRDR, quinolone resistance-determining region; NA, nalidixic acid; LVX, levofloxacin; AMP, ampicillin; AZI, azithromycin.

transmission of *H. influenzae* from child to adult or among siblings in household setting is well known (13). We do not have any comparative figures for isolates from adults. If adults are a source of the quinolone-resistant isolates, one would expect greater resistance rates in adults than children.

Detection of *H. influenzae* isolates from children with a first-step mutation in *gyrA* affects whether the fluoroquinolones should be approved for pediatric indications (14). So far, the main concerns among the scientific community have centered on the selection of fluoroquinolone-resistant pneumococci. Unlike adults, children frequently carry pneumococci in the nasopharynx and at high density. If the fluoroquinolones are used widely in children to treat infections such as salmonellosis, recurrent otitis media, and urinary tract infections, the selection of mutational resistance to the fluoroquinolones will likely occur more rapidly among children than among adults. Once resistance is selected, fluoroquinolone-resistant strains could disseminate rapidly and widely in the community by cross-transmissions in groups attending daycare centers and schools. Our finding thus highlights the need to monitor resistance not only among the infecting organisms being treated, but also the need to monitor colonizing bacteria in the same or other body sites that were also exposed to antimicrobial agents.

Our data have shown a low incidence (0.9%) of decreased levofloxacin susceptibility due to *gyrA* mutations among strains of *H. influenzae* isolated from children in Hong Kong. This finding warrants public health concern. Given that the fluoroquinolones might be increasingly used as a rescue therapy for certain pediatric infections that do not respond to other agents, surveillance of this type of resistance mechanism must be enhanced. In this regard, we have found that resistance to nalidixic acid (MIC ≥ 64 μg/mL) or reduced susceptibility to levofloxacin (MIC ≥ 0.125 good μg/mL) might be useful surrogates. After we submitted this manuscript, similar observations on the laboratory detection of deceased susceptibility due to *gyrA* and *parC* mutations were reported (15); thus, our findings were corroborated.

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International Conference on Women and Infectious Diseases

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On February 27–28, 2004, scientists, clinicians, researchers, women's health advocates, educators, policymakers, and representatives from nongovernmental organizations and community-based organizations gathered in Atlanta for the first International Conference on Women and Infectious Diseases (ICWID): From Science to Action. The Office of Minority and Women's Health of the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), spearheaded the conference. It was cosponsored by the World Health Organization, the Pan American Health Organization, the Department of Health and Human Services (DHHS), and the American Society for Microbiology.

The broad ICWID steering committee included representatives from the DHHS Office on Women's Health, the National Institutes of Health Office for Research on Women's Health, the National Institute of Allergies and Infectious Diseases, the National Institute for Child Health and Human Development, the Fogarty Center, and the Office of Women's Health of the Health Resources and Services Administration. Academic, community-based, and philanthropic organizations as well as numerous CDC entities were involved. The conference's goal was to enhance prevention and control of infectious diseases among women worldwide. The conference's 400 attendees from 25 countries (both industrialized and developing nations) and 30 U.S. states recognized the need for a forum to address the complex set of concerns and issues surrounding women and infectious diseases.

Julie Gerberding, director of CDC and administrator of the Agency for Toxic Substances and Disease Registry, opened the conference with an overview of the impact of infectious diseases on women. The address reminded listeners of the female face of infectious diseases: women may be biologically more susceptible to certain infections and suffer more severe complications. Other keynote speakers included Paul DeLay of the Joint United Nations Programme on HIV/AIDS, Carol Bellamy of the United Nations Children's Fund, and Mirta Roses Periago of the Pan American Health Organization.

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Marian McDonald

Dr. McDonald serves as associate director for Minority and Women's Health, National Center for Infectious Diseases, CDC. She chaired the International Conference on Women and Infectious Diseases: From Science to Action, held in Atlanta February 27–28, 2004. She has worked in women's health and minority health for 3 decades.

Martha Anker

Ms. Anker has just retired from 25 years at the World Health Organization but continues to be active in research. She has researched gender issues throughout her career, most recently working on the effects of sex and gender on disease transmission and control during outbreaks of epidemic-prone infectious diseases.

Carolyn Deal

Dr. Deal is chief of the Sexually Transmitted Infections Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health. She has worked at Walter Reed Army Institute of Research, the Office of Vaccines Research and Review, and the U.S. Food and Drug Administration.

Alison Mawle

Dr. Mawle serves as vaccine coordinator for the National Center for Infectious Diseases, CDC. She began her career at CDC more than 20 years ago as an immunologist in the fledgling AIDS immunology laboratory.

Siobhán O'Connor

Dr. O'Connor serves as assistant to the director for Infectious Causes of Chronic Diseases, National Center for Infectious Diseases, CDC. She is active in developing the research agenda for and a strategic approach to this cross-cutting area, with known and potentially unrecognized impact on women.

The theme of the conference was "From Science to Action." In 35 sessions, attendees discussed the practical application of scientific knowledge in areas such as HIV, infectious causes of chronic diseases and other infectious disease–chronic disease relationships, gender roles in infectious disease transmission and prevention, sexual coercion and its effect on infectious diseases in women, sexually transmitted diseases, health disparities, healthcare workers and caregivers, immunization, effective community-based strategies, the role of cultural competence in women's health, and more.

The Bill and Melinda Gates Foundation sponsored 26 ICWID scholarships, which allowed persons from nongovernmental organizations and community-based organizations from 10 countries and four continents to attend who otherwise would not have had the opportunity. These ICWID scholars will amplify the conference's impact by taking the knowledge and insights gained back to their home countries and organizations.

The conference successfully illuminated the female face of infectious diseases. While celebrating successes in the prevention and control of prenatal and neonatal Group B *Streptococcus* infections and achievements in other arenas, participants emphasized the many challenges remaining for the future. With the continuation of such efforts, the newly spotlighted female face of infectious diseases can also be the face of hope and progress.

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The Woman at the Dig

Tired from running a combine
all day through acres of wheat,
alone in front of the TV, I pay
attention because the show's about
scientists digging up an ancient site.
I have no special interest in bones,
pottery, spearheads, or prehistoric
garbage dumps, and I always look past
the man describing animal migrations,
burial rites, or building design and try
to catch a glimpse of the women
working at the site – one of them
might be wearing cut-off jeans
and a halter top, clearing a patch
of ground with a trowel or brush.
These women are all experts.
You can tell by the way they look
at a bone chip or a pottery shard
they understand worlds about
the person who left it. Sifting soil,
they show more grace than contestants
in a Miss Universe pageant.
Years from now, when these farms
are ancient history, an expedition
with such a woman might come along.
I could drop something for her to find,
a pocketknife, a brass overalls button.
If only she could discover my bones.
My eyes would be long gone,
But I can see her form coming into focus
above me as she gently sweeps aside
the last particles of dust – her knee, thigh,
hip, shoulders, and finally, set off by sky
and spikes of sunlight, her face – a woman
who recognizes what she's found.

Leo Dangel (b. 1941)
From The Crow on the Golden Arches, Spoon River Poetry Press, 2004. Reprinted with permission.

Women and Infectious Diseases

Julie L. Gerberding*

Julie L. Gerberding

Social, economic, environmental, and demographic changes during the 20th century have affected the health of women. Many of the changes have benefited women's health, but some have had deleterious effects. Infectious diseases pose an especially formidable threat to women, claiming >15 million lives around the globe each year (1). For many infectious diseases, women are at higher risk and have a more severe course of illness than men for many reasons, including biologic differences, social inequities, and restrictive cultural norms. These are often the same factors responsible for the disproportionate disease incidence among vulnerable populations throughout the world. Efforts to recognize and reduce health disparities among women have particular relevance for global health.

HIV and AIDS in Women

In addition to hunger, lack of education, and environmental and sociocultural constraints, HIV/AIDS and malaria, along with tuberculosis, continue to disproportionately affect and further weaken the condition of women in many of the world's poorest regions. Recent estimates indicate that more than half of the estimated 38 million cases of adult HIV infection worldwide are in women (2). Moreover, the social, economic, and psychologic effects of the disease are more severe for women. When their partners or fathers die, women often lose economic rights. A Ugandan survey found that one in four widows reported losing their property after their partner died (3).

In sub-Saharan Africa, the region most affected by HIV, women are 30% more likely than men to be HIV-infected (2). The largest gender difference occurs among younger age groups. New HIV infections among women are also on the rise in the United States. An analysis of newly diagnosed HIV infections that occurred in 29 states from 1999 to 2002 showed that more than one third (35%) of cases resulted from heterosexual contact; among these heterosexually transmitted infections, almost two thirds (64%) occurred in women (4). Similarly, a recent analysis of New York City's HIV reporting data found that 35% of new HIV diagnoses in 2001 were in women, compared with 28% before 2001 (5).

HIV infection in women has obvious implications for the health and well-being of children. HIV infection can be transmitted perinatally, and increasing numbers of children—estimated at ≈12 million—are orphaned by the disease (2). Although preventing HIV transmission from an infected mother to her infant has become feasible because of effective antiretroviral treatment regimens and has met with great success in many parts of the world, services that prevent mother-to-child transmission are severely limited in low-income countries. Similarly, although combination antiretroviral therapy offers the potential to manage the disease as a chronic, treatable condition, access to such treatment is primarily limited to persons in high-income countries, which excludes the most severely affected regions. As an example, ≈4.1 million persons in Africa are in need of such therapy, but <2% have access to the drugs (6).

Preventing new infections is fundamental to stopping the spread of HIV. Attaining this goal requires that all persons have information about the disease and know their infection status, a formidable challenge in both low- and high-income countries. Such information can help uninfected persons remain free of the disease and help those who are infected gain access to treatment and prevent transmission to their partners. Fortunately, several broad-based national and international initiatives have been taken to meet these challenges. For example, the President's Emergency Plan for AIDS Relief is a 5-year, $15 billion commitment to treat HIV infection and prevent new infections in Africa and the Caribbean. Other undertakings include the United Nations' Global Fund to Fight

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AIDS, Tuberculosis, and Malaria and "The 3 by 5 Initiative," a detailed, multicountry plan developed by the World Health Organization and the Joint United Nations Programme on HIV/AIDS to provide antiretroviral treatment to 3 million HIV-infected persons in developing countries by the end of 2005.

Malaria in Women

Malaria is another infectious disease threat that disproportionately affects women; it causes serious illness in pregnant women and children <5 years of age. Every year, malaria kills 1.5 million to 2.7 million persons and adversely affects another 300,000 to 500,000, mostly in Africa (7,8). Pregnant women suffer decreased immunity to malaria, which more than doubles their chances of contracting and dying of the disease (9). Pregnant women who contract malaria have an increased risk for severe maternal anemia. The consequent impaired fetal growth contributes to low birthweight in newborns. Malaria during pregnancy causes as many as 10,000 maternal deaths each year, 8%–14% of all low birthweight babies, and 3%–8% of all infant deaths in certain parts of Africa (9).

Other Infectious Diseases in Women

In addition to HIV, women are more susceptible to other sexually transmitted diseases (STDs) and their long-term complications. In the United States >50% of preventable infertility is related to STDs (10). In addition, most sexually transmitted pathogens can be passed to the fetus or infant, sometimes with fatal consequences.

Longitudinal studies show that women are also at greater risk for active disease from *Mycobacterium tuberculosis* infection (11). Case-fatality rates are likewise higher in women. Reasons include decreased immune function attributed to poor nutritional status and delays in seeking care, both of which can be a function of gender.

The tropical parasitic disease schistosomiasis presents special concerns for women. Among parasitic diseases, schistosomiasis is second to malaria in prevalence; it affects >200 million persons in 74 countries (12). In affected areas, women are at greater risk for the disease than men because of their increased exposure to contaminated water through domestic work, such as washing clothes and preparing food. Consequences of the disease are more severe in women than in men. Female genital schistosomiasis, often misdiagnosed as an STD, can cause tumors, ulcers, and infertility and may actually increase the risk for STDs (13).

Infectious Diseases in Pregnant Women

Pregnancy complicates the impact of many other infectious diseases. Each year in the United States, ≈20,000 infants are born to women infected with hepatitis B virus (HBV) (14). Without postexposure prophylaxis, ≈6,000 of these infants would become chronically infected with HBV, and ≈1,500 would die prematurely of chronic liver disease. To address this problem, perinatal HBV prevention programs screen pregnant women for HBV and follow-up with vaccination of newborns. Hepatitis C virus can also be transmitted during pregnancy, although the rate of infection appears lower than that of HBV. Hepatitis E virus can also have severe consequences if acquired during pregnancy, especially during the third trimester (15,16). This virus has been associated with increased risk for spontaneous abortions and stillbirths as well as fulminant hepatitis in both mothers and infants (16).

Another serious maternal infection is group B streptococcus (GBS). GBS can be transmitted from mother to baby during pregnancy or during labor and delivery. During the 1990s, prevention efforts involving intrapartum antibiotic prophylaxis dramatically lowered the incidence of disease (17). However, GBS remains a leading infectious cause of illness and death among newborns in the United States (18,19).

Reducing Health Disparities in Women

Women are caretakers and brokers of health for their families. These roles can increase their risk for infectious diseases and increase obstacles to adequate and timely treatment. Seeking health care can be the first step to identifying and treating a host of illnesses affecting women and their families. Therefore, innovative ways to reach women at risk, including developing new research agendas to identify and address gender differences in infectious disease, are especially needed.

Reducing health disparities for women requires a multidisciplinary global effort to combat the root causes of these disparities—social, economic, and educational inequities that fuel the spread of diseases and perpetuate poverty throughout the world. Although much remains to be done, commitment to reduce these disparities on behalf of the international community is increasing. In addition, participants at the International Conference on Women and Infectious Diseases also play an important role in these efforts through their broad range of expertise and commitment to improving global health.

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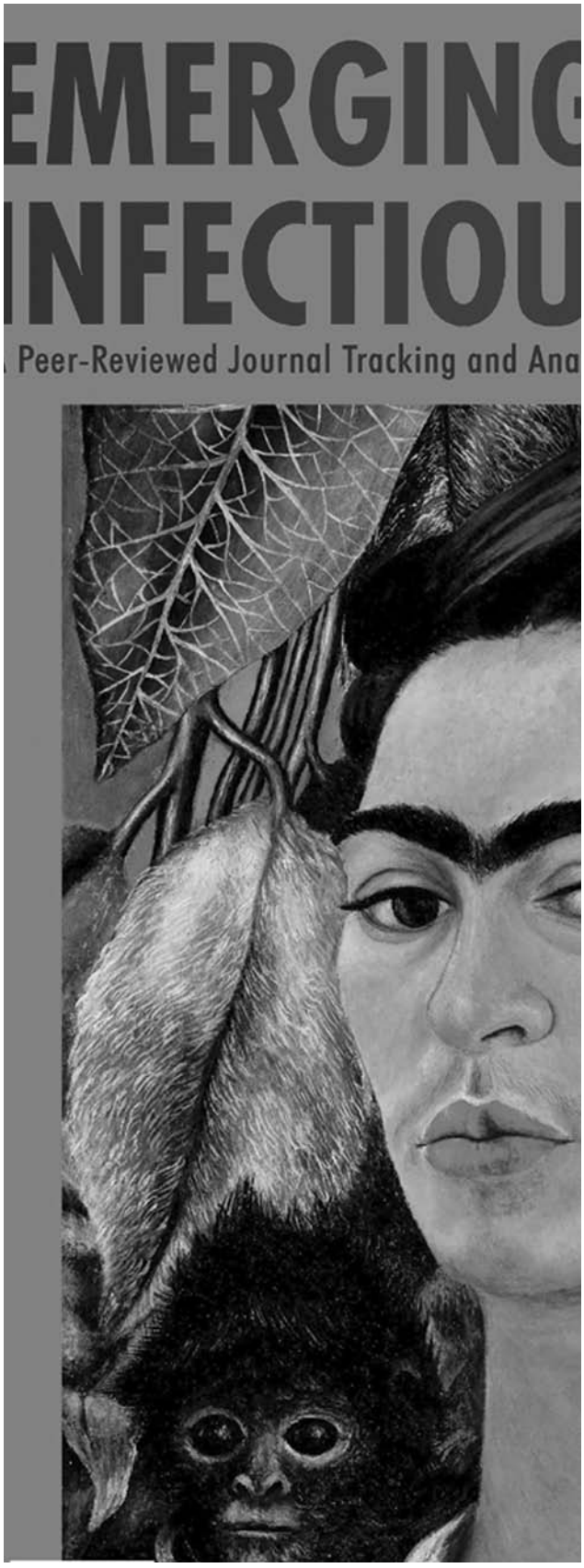

Steps for Preventing Infectious Diseases in Women

Mirta Roses Periago,* Ricardo Fescina,* and Pilar Ramón-Pardo*

Communicable diseases account for approximately 25% of deaths in most Latin American and Caribbean countries; illness from communicable diseases reaches 40% in developing countries. Mainly affected are poor women in rural areas. A medical approach is not sufficient to implement effective infectious disease prevention strategies in women, which would offset these numbers. Health policies must be changed, and social restrictions that circumscribe women need to be eliminated. In the long run, the only solution is to improve women's socioeconomic status. The following three steps are necessary for developing a prevention strategy: 1) a gender perspective must be incorporated into infectious disease analysis and research to target policies and programs. Data collected must be disaggregated by sex, age, socioeconomic status, education, ethnicity, and geographic location; 2) models must be developed and implemented that address gender inequities in infectious diseases in an integrated manner; and 3) outreach activities must be supported, using information, education, and communication strategies and materials for advocacy and training. Active participation of civil society groups is key to translating the strategy into specific interventions.

"…as the Millennium Declaration made clear, gender equality is not only a goal in its own right; it is critical to our ability to reach all the others."

—Kofi Annan, Secretary-General of the United Nations

In most Latin American and Caribbean countries, communicable diseases cause approximately 25% of deaths. This overall rate varies from country to country; it is higher in less developed countries. Communicable diseases; perinatal conditions and complications of pregnancy, childbirth, and postpartum; and nutritional diseases represent approximately 5% of the illness in industrialized countries. That percentage climbs to 40% in developing countries and reaches 50%–60% in some areas where HIV/AIDS epidemics are widespread (1). As a consequence, a large decrease in deaths of women would be expected if infectious diseases decreased through effective prevention strategies.

In the developing world, infectious diseases mainly affect women in rural areas (2). Poor women are at a greater disadvantage for coping with these diseases because of their social environment. Several infectious diseases can be successfully treated with available drugs, and well-known methods are available to prevent many diseases. Much could be done to improve health services, including implementing earlier case detection and better treatment regimens.

A medical approach will not succeed by itself, however. Success will only be achieved when coupled with behavioral changes and a breakdown of social barriers that restrict women. In the long run, the only solution is to improve women's socioeconomic status; this requires educating them, which, in turn, accelerates their social and economic progress.

Women and Communicable Diseases: A Situational Analysis

An examination of health policies over the last 2 decades in most of the Americas illustrated the following points: 1) Women's health, in and of itself, rarely has been at the forefront of international development programs or national health planning and policies. 2) The focus on women's health in developing countries has been motivated largely by other concerns. As a rule, women have been viewed as the vehicles through which specific goals, such as family planning and child survival, could be achieved, rather than as the primary beneficiaries of or the partners in development programs. 3) The global agenda for preventing communicable diseases among women rests on two premises, namely, that understanding women's health in developing countries, particularly the health risks they face, is important for instituting appropriate interventions to address women's specific health needs, and that women's participation in health promotion and disease prevention is key to the health of families and communities worldwide.

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Evidence collected in studies conducted in various countries shows that macrodeterminants—such as gender, ethnic origins, or race—play a major role in the degree of access to services and in the health status of populations. A study of racial inequities in health conducted in Brazil (3) examined infant deaths in relation to both race and level of education of the mother. For illiterate mothers, infant death rates neared 120/1,000 for black women, 110/1,000 for mulatto and dark-skinned women, and 95/1,000 for white women. Among mothers who had ≥8 years of education, the rates were much lower—82 for black women, 70 for mulatto and dark-skinned women, and 57 per 1,000 for white women. These rates indicate disparities according to race. Black women need 4–7 years of education before the death rates of their infants are as low as those of infants born to uneducated white women, demonstrating the strength of the effect of ethnically based discrimination in health.

In Latin America and the Caribbean, the death rate in the population aged 15 to 59 years old is higher in men than in women; in the poorest groups, however, the risk for death in men and women is nearly equal. In 13 Latin American and Caribbean countries, the death ratio between poor and not-poor populations is three times higher for men and seven times higher for women.

The higher ratio for women is partially explained because the number of deaths during the pregnancy and childbearing years is significantly higher in those at lower socioeconomic levels. This fact captures one of the greatest inequities in health, given that most childbirth-related deaths are preventable. Infections after childbirth and after abortions take a considerable toll in countries where maternal deaths are >50 per 100,000 live births.

An estimated 25 million cases of sexually transmitted infections (STI) occur each year in the Americas. An estimated 330,000 pregnant women have positive serologic test results for syphilis every year. The 3.1% maternal positive serologic rate suggests that this disease is a major contributor to illness in women and infant deaths. Moreover, the HIV infection rate in the Caribbean is rising faster among women than among men. Of all the HIV infections in the region, women account for 25% in Latin America and 35% in the Caribbean; the sex ratio in those countries where the epidemic is widespread approaches 1:1.

Communicable diseases in developing countries are largely diseases of poverty (2). The poor are at most risk because of their precarious living conditions, often inadequate health services, and lack of access to care. In many cultures, the lower value assigned to women translates into higher levels of suffering, with infectious diseases accounting for 33% of all causes of death among women (4).

A long history of gender discrimination also leads to inequalities that perpetuate a lack of access to resources and services for women and their children. Almost 70% of the 1.2 billion people worldwide living in extreme poverty are women (5), who experience more illness and are less likely to receive medical treatment. Women report 15% more health problems (diseases and accidents) than do men. Yet, women's use of the health services is only 2% higher than men's. Furthermore, this tendency for women to have even this modestly greater use of health services than men disappears in the lowest income quintile, where, paradoxically, the gender gap in health need is widest.

Health data from Guatemala (6) indicate that there is a persistent gap in access to health care between indigenous and nonindigenous groups. Indigenous groups get less prenatal care than nonindigenous groups (45% vs. 67%, respectively). For example, tetanus vaccination rates for indigenous and nonindigenous groups are 46% and 62%, respectively.

Ethnic origins, too, function as an invisible barrier that hinders access to health services. In the Municipality of São Paulo, the health system offers retrovirus treatment for HIV patients, which has decreased death rates. A closer look at the heath statistics of the municipality's department of health 2003 (7), however, shows that the risk for death from HIV/AIDS among black women is four times higher than that among Caucasian women.

Gender Framework for Infectious Diseases

The World Health Organization has developed a framework (8) that outlines the parameters of a gender approach for understanding the differential impact of communicable diseases on women and men (Figure). Few studies have focused on the economic and productive impact of infectious diseases, considering the cost of reduced or lost productivity and expenditures on drugs and health care at the individual worker level. For the most part, these studies have failed to capture the economic impact of disease within the household. And it is precisely at the household level that women are most affected, both as caregivers and as patients.

In most developing countries, unemployment is higher among women, and when women are employed, their salaries are generally much lower than men's (9). These conditions mean that women have fewer resources than men, yet spend more of their own income on health care for their children and other family members. Structural adjustment programs have placed additional burdens on women. Reductions in state-supported healthcare programs have resulted in reduced access to health care for the poorest populations, and long waits in clinics have serious repercussions for women's time for other activities.

The framework also includes many social determinants of infectious diseases, such as domestic and social roles and responsibilities, cultural norms affecting exposure,

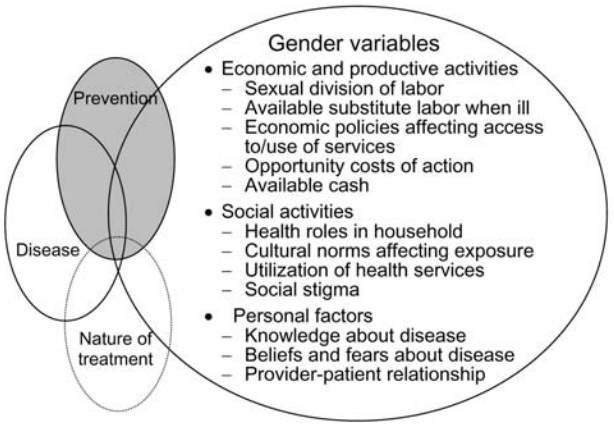

Figure. Framework on gender variables developed by the World Health Organization Special Programme for Research and Training in Tropical Diseases.

available support networks, social stigmas, use and quality of health services, and decision-making power within the household and community. In many cultures, men are still given better care within the family, as well as outside. Women's lower status in the household affects their access to information about health and preventive measures, as well as their ability to seek treatment. Evidence suggests that women's ability to make decisions has considerable influence on the health of their children. When health messages meant for women are directed to men, their direct influence on women's understanding and behavior may be greatly diluted.

On the other hand, when men have taken responsibility for their children's health care, results have been dramatic. In Ghana, for example, the fathers' participation in the decision to immunize their children not only increased vaccination rates but also led to earlier immunization and more timely completion of the immunization schedule (10). These findings show that health programs can be improved by educational messages that promote the sharing of child care and are directed to the family as a whole, not just to the mother, as has traditionally been done.

Physicians' tendency to release knowledge only when they consider it necessary has been found to curtail women's understanding and adherence to medical advice. For example, a study in rural Bolivia found that women living in areas where Chagas' disease was endemic were able to recognize triatomine bugs and had seen them in their houses, but 59% did not know that they could transmit disease (11). Health education programs are based on modern biomedical explanations that often are too abstract for persons to link to their own environment. In addition, health authorities do not sufficiently build upon local perceptions of disease and disease transmission.

Men and women experience disease differently in important ways. These differences can be grouped into social, economic, and personal consequences. Studies of the economic consequences of malaria in Colombia (12) found that women waited longer to seek treatment because their household work was essential for the functioning of other family members. They also took longer to recover than men and often returned to work while still debilitated. Men's illnesses were diagnosed and treated earlier, and men received better care while recovering. Although women or other family members took over the work of the men who became ill, much of women's work was left undone until they could return to it after recovering.

Gender differences in the social and personal consequences of infectious diseases are illustrated by studies on stigmatizing diseases such as leprosy or HIV/AIDS. Generally, women suffer greater discrimination and are more likely to be held responsible for their illness and to be isolated from their families and communities (13).

Response of the Pan American Health Organization (PAHO)

An Integrated Model To Address Gender Inequities

Since the 1990s, PAHO's Gender and Health Unit has worked at the regional, national, and community levels to advocate for, and involve communities in, formulating gender-sensitive health policies. This unit has developed an integrated model to address gender inequities. The model was initially validated by using gender-based violence, but it can be adapted to apply to communicable diseases. The model involved communities providing care and support to persons affected by gender-based violence through networks that plan, implement, and monitor several activities. First, health services are often the initial contact point, so health providers are trained to screen women for gender-based violence during routine healthcare visits. A situation analysis then assesses the prevalence of gender-based violence in the community and identifies organizations and persons who help victims. Community organizations and leaders are then mobilized into support and service networks that meet to plan activities. Finally, replications of the community networks at the regional and national levels advocate for policies, legislation, and resources.

Millennium Development Goals

The United Nations Millennium Declaration (2000) prioritizes development and freedom for all the peoples of the world. As a way to monitor national and international progress in this regard, the United Nations and other international organizations formulated the Millennium Development Goals, which have rapidly become the primary focus of international development efforts as coun-

tries and organizations strive to meet them.

Within these goals, gender equality and women's empowerment are acknowledged as central to development through goal number 3. However, since gender is an issue that affects practically every aspect of people's lives, it has also becomes central to achieving the remaining seven goals.

Gender-based Violence and STI

A growing number of studies have documented the high prevalence of intimate partner and sexual violence against women worldwide. This violence increases women's vulnerability to HIV and STI both directly, through forced sex, and indirectly by constraining their ability to negotiate sexual contact and the use of condoms. In addition, sexual abuse during childhood has been associated with high-risk behavior later in life, which also increases the risk for HIV infection (14).

PAHO is promoting primary prevention of STI/HIV/AIDS through several strategies. These include increasing access to reproductive health services; reducing violence against women; protecting women's rights and their property; ensuring women's and girls' access to health services and treatment; and supporting educational efforts to combat stigmatization and discrimination.

Infectious disease prevention must include several steps. First, a gender perspective must be incorporated into infectious disease analysis and research so that policies and programs can be targeted more effectively. An initial step should be the collection of data disaggregated not only by sex, but also by age, socioeconomic status, education level, ethnicity, and geographic location. Second, models that address gender inequities in infectious diseases in an integrated manner need to be developed and implemented. Third, support outreach activities, using IEC (information, education, and communication) strategies and materials for advocacy and training, need to be set up.

Next Steps in Prevention

The failure to acknowledge that gender and poverty interact to place women at particular health risk contributes to stereotypes used in infectious diseases research and control (15). Gender stereotypes can be reflected in the delivery of health services in two ways. First, women and men have different vulnerabilities to infectious diseases that have to do with biologic, social, and cultural factors. Many times, similar prevention strategies are provided for men and women, even when their needs are not the same (e.g., HIV/AIDS prevention campaigns directed to male and female adolescents). Secondly, infectious disease prevention and control programs often reinforce gender stereotypes. For example, programs often focus exclusively on mothers to be responsible for children's health, oral rehydration therapy, or supervision of drug therapy for tuberculosis.

Gender interacts with biologic differences and social factors. It affects access to health care, health-seeking behavior, health status, and the way health policies and programs are developed and implemented (16). More than a variable, gender is a construct that underpins the way health sciences and the health system are organized (17). Enormous changes need to take place in the study and control of infectious diseases. Social and behavioral scientists have long argued that these diseases will not be eliminated without attention to social inequalities.

The key for putting gender values firmly in place within prevention strategies is a change of philosophy at all levels of the health sector, from the political to the health-care levels. The traditional male model for prevention needs to be seen as inadequate. Rather, both gender equity and equality are required to attain health for all. The steps for developing a gender-sensitive prevention strategy include political commitment, knowledge building, and development of the technical capacity and awareness to implement and evaluate preventive strategies

Political Commitment

Political commitment is necessary to empower women and to address gender inequalities. This commitment should translate into prevention strategies specifically targeted to women. Integrating a gender analysis into health policies and programs is necessary for achieving the Millennium Development Goals.

These goals acknowledge gender equity as an important prerequisite for development. In fact, the third Millennium Development Goal deals specifically with gender (18). A core strategy in working to achieve these goals is ensuring that a gender-sensitive approach is incorporated into strategies and interventions for infectious diseases (e.g., for HIV/AIDS, tuberculosis, and malaria).

Social civil organizations, such as the "Red de Salud de la Mujer de Latinoamérica y el Caribe," are important stakeholders to advocate for political commitment and to foster the implementation of norms and policies. Political commitment should also be translated into the necessary budget allocations, to be incorporated as a separate line item in programs, to allow planning, implementation, and training in a gender-sensitive approach to preventing infectious diseases.

Gender should be mainstreamed through each health organization, from the World Health Organization to governmental and nongovernmental organizations. Women's involvement in policy and program development at the highest levels will facilitate the integration of gender into

health programming and policymaking.

Knowledge Building

Epidemiologically Disaggregated Data

Studies demonstrate that gender analysis provides a more comprehensive understanding of the epidemiology of health problems, including that of infectious diseases. Analysis of health determinants, impact of disease, and health-seeking behavior should be disaggregated by sex to determine the different factors that affect women. Health statistics based on official data from health services may underestimate female illness and death from infectious diseases because women often do not go to these centers for detection and treatment of their health problems, as has been shown in a study on cutaneous leishmaniasis in Colombia (19).

Research

Much of the gender research in infectious diseases is outdated, limited, or inconclusive. Socioeconomic and health factors in relation to infectious diseases and gender have been established, but epidemiologic data are sparse. For example, tuberculosis is one of the most important causes of death among women, killing more women that all maternal causes of death. Sex-related research on tuberculosis is lacking, however (20). To address the impact of sex in infectious diseases, we need to assess the magnitude of the problem, study sex differences, and then pilot interventions to address the problems identified.

Gender also affects the research questions asked, the way data are examined, and the way male or female clients are treated when they come to the health center. Gender is more than a variable to be manipulated; it is an organizing principle of society. The mainstreaming of gender-sensitive research needs to be linked to the mainstreaming of gender sensitivity in infectious diseases programs, including prevention programs.

Development of Evidence-based Strategies and Interventions Addressing Women's Specific Needs

Medical and social scientists must seriously consider gender, its interaction with physiologic and immunologic factors, and the ways in which men and women can be protected from or put at risk for communicable diseases by that interaction. Interventions in communicable diseases must be planned with an understanding of the way in which gender influences the degree to which men and women, as persons and population groups, have access to and control of the resources needed to protect their own health and that of family and community members. Those involved in infectious disease prevention—be they working in vector control, vaccine and drug development, improvement of surveillance and monitoring systems, or health work in countries with endemic diseases—need to be aware that gender structures the way they assess problems.

Operational research is needed to determine how best to ensure that global strategies (e.g., the directly observed treatment short course [DOTS], the Roll Back Malaria initiative, the so-called 3 by 5 Initiative) are gender-sensitive. After research results have been analyzed, interventions should be planned, implemented, and evaluated. A gender equality approach should be promoted in all preventive activities, from an awareness campaign of malaria to an HIV voluntary counseling and testing intervention.

Development of Technical Capacity and Awareness To Implement and Evaluate Preventive Strategies

Linking gender to training and performance of health professionals is critical. An understanding of gender and its implications for health and health-seeking behavior should be incorporated into training of health professionals and development of health sector responses.

Promotion of girls' education and women's empowerment should be addressed through interagency collaboration. Research has shown repeatedly that health information provided to rural women in developing countries is incomplete and frequently ill-adapted to their priorities and needs. Many such women have not benefited from formal education and are unable to read. They cannot understand the writing on health education posters or directions on medications. Conducting a gender analysis of epidemiologic data improves the detection and treatment of infectious diseases in underreported groups (21), which, in turn, provides the cornerstone for designing adequate preventive strategies.

Conclusion

When planning and implementing infectious disease prevention's strategies, gender is an issue that has been neglected by infectious disease programs. A gender-based approach to communicable diseases helps to elucidate the various factors involved in the impact of infectious diseases in the population. After more than a decade of work on gender approaches, a new method is needed to translate the frameworks and theories into specific public health interventions so that gender inequalities are minimized.

Partnerships with the civil society should advocate for decreasing gender inequalities in health, including infectious diseases. This advocacy can foster the political commitment to institutionalize policies in norms and protocols that would decrease these inequalities. Agencies should promote building technical capacity and gender-sensitivity awareness in both developing and industrialized countries. Incorporating a gender perspective into health policies and

programs is necessary for improving the coverage and effectiveness of health programs.

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Barriers to Infectious Disease Care among Lesbians

Jeanne M. Marrazzo*

Despite the considerable number of women in the United States who identify as lesbian, few data exist that address lesbians' health needs. The Institute of Medicine emphasized that data on sexually transmitted infections, Pap smear screening, and cervical dysplasia among lesbians were needed to guide clinical practice, policy development, and patient education. Use of surveillance data for this purpose is limited because risk classifications exclude same-gender sex among women or subsume it under behavior considered as higher risk. However, sexual transmission of human papillomavirus, HIV, *Treponema pallidum*, and *Trichomonas vaginalis* between women has been reported. Data indicate that lesbians receive routine Pap smear screening less frequently than is optimal. Moreover, lesbians commonly report previous pregnancy, induced abortion, and hormonal contraceptive use. Education of lesbians and their care providers should counter assumptions that sex between women confers no risk for transmission of sexually transmitted infections, and lesbians should receive Pap smears according to current guidelines.

A causative link between a patient's sexual orientation and access to healthcare is not evident. Why should identification as a lesbian or practice of same-sex behavior affect a patient's access to infectious diseases–related care? We discuss data to support this connection and make appropriate recommendations. Because this article discusses a subset of women defined by their practice of sex with other women, it will focus primarily on sexually transmitted infections (STIs) and their consequences. For the sake of simplicity, we will use the term "lesbian" to refer to a woman who engages in sex with another woman, and thus represents the axis of sexual behavior, which may not necessarily be congruent with self-defined sexual identity (1).

In the United States, estimates of lifetime same-gender sexual behavior among women are 8% to 20%, and 1.4%–4.3% of all women may currently be sexually active with other women (1,2). An estimated 2.3 million women specifically describe themselves as lesbian (3). Despite these considerable numbers, relatively little data are available on important health outcomes for these women, including prevalence of STI, HIV, and cervical cancer. Until recently, the major national women's health studies did not collect information on same-sex behavior or sexual identity (4). In its 1999 report, Lesbian Health: Current Assessment and Directions for the Future, the Institute of Medicine emphasized that more data were needed on STIs, Pap smear screening, and risk for cervical cancer in lesbians (3).

Sexual Behavior and STIs

Attempts to use national or local surveillance data to estimate the risk for STI transmission between women are limited by the fact that many risk classification schemes have either excluded same-gender sex among women or subsumed it under a hierarchy of other behaviors viewed as higher risk. Moreover, few, if any, state or local STI reporting systems routinely collect information on same-sex behavior among women. The available data are derived from two sources: small studies that have directly measured prevalence of common STIs, usually among clinic attendees or self-referred study volunteers, and surveys that have queried lesbians about their self-reported STI history. Many of these studies have also assessed lesbians'self-report of sexual practices. Taken as a whole, these data indicate that the risk for STI transmission between women depends on the specific STI under consideration, and the sexual practices involved.

Some sexual practices, including oral-genital sex, vaginal or anal sex using hands, fingers, or penetrative sex toys, and oral-anal sex, are commonly practiced by female sex partners (5–7). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex toys, present a plausible means for transmission of infected cervicovaginal secretions. This concept is most directly supported by reports of metronidazole-resistant trichomoniasis and genotype-concordant HIV, which have been sexually transmitted between women who reported these behaviors (8,9). Reports of *Chlamydia trachomatis*

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and *Neisseria gonorrhoeae* transmission between women are anecdotal and largely unpublished; however, approximately 3%–5% of respondents to surveys assessing lesbians' lifetime history of these STIs indicate that a chlamydial infection had been diagnosed by a healthcare provider. Among 6,146 respondents in the National Lesbian and Bi Women's Health Survey, conducted in the early 1990s, women reported contracting an STI from a female partner (including herpes by 135 persons, chlamydia by 102, genital warts by 100, gonorrhea by 16, hepatitis by 9, and HIV by 1) (10). Although self-report of STI history is often inaccurate (as is attribution of STI to a specific source partner), these data indicate that the respondents sought care for perceived genitourinary abnormalities and received a diagnosis that indicated the provider had reason to suspect an STI. The most important bacterial STI for which more precise data are needed is *C. trachomatis* infection. Although the rate of transmission of STIs between women is probably low relative to that of transmission from men to women, a substantial proportion of lesbians, including those who self-identify as lesbians, and especially younger women most at risk for chlamydial infection, may continue to have sex with men (11).

Transmission of common viral STIs, especially human papillomavirus (HPV) and herpes simplex virus (HSV) infections and of *Treponema pallidum*, the causative agent of syphilis, requires only skin-to-skin or mucosa contact, which can easily occur in the context of lesbian sex. Equally important, most lesbians (53%–99%) have had sex with men, and many (21%–30%) continue to do so (11); they may acquire viral STIs from men and subsequently transmit them to female partners. In addition to case reports, two studies have detected HPV DNA by PCR-based methods in 13% to 30% of lesbians (6,12). Samples obtained from the cervix, vagina, and vulva all demonstrated HPV DNA, and no one anatomic site accounted for most infections. In one study, HPV DNA was present in 19% of lesbians who reported no previous sex with men (6). Importantly, both high- and low-grade squamous intraepithelial lesions (SIL) were detected on Pap smear testing, and they were found in women who reported no previous sex with men. Using capture enzyme-linked immunosorbent assay (ELISA) to measure type-specific antibodies to HPV, we found that 62 (47%) of subjects were seropositive for antibodies to HPV 16, and 83 (62%) were seropositive for HPV 6 (6,13). Of note, HPV seropositivity among women who reported previous or current sex with men did not differ from that of women who reported no previous sex with men. Given this, and the fact that SIL has been observed in women who reported no previous sex with men, one can conclude that high-risk and low-risk types of genital HPV are sexually transmitted between women and that lesbians should undergo Pap smear screening according to current national guidelines.

Most cases of genital herpes are caused by HSV-2, although recent reports indicate a consistent trend toward more HSV-1–related genital disease (14). When Western blot assay was used to detect type-specific antibodies among 392 women in the Seattle Lesbian Health Study, antibodies to HSV-1 were detected in 182 (46%), and to HSV-2 in 31 (8%) (15). Most HSV-2 seropositive persons (71%) reported no history of genital herpes, and HSV-1 seroprevalence increased significantly as number of female partners increased. Older age predicted a higher seroprevalence of both HSV types, and HSV-2 seropositivity was associated with a reported history of having had a male partner with genital herpes (but not with number of previous male sex partners). Of 78 women reporting no previous sex with men, 3% were HSV-2 seropositive. Although genital transmission of HSV-2 between female sex partners occurs in a relatively inefficient manner, lesbians' relatively frequent practice of orogenital sex may place them at somewhat higher risk of genital infection with HSV-1, a hypothesis supported by the association between HSV-1 seropositivity and previous number of female partners.

Although *T. pallidum* infection is relatively uncommon, compared to the viral STIs discussed above, sexual transmission between female partners has recently been reported (16). Because some lesbians who choose to have sex with men may be more likely to choose bisexual men for partners (17,18), healthcare providers should keep in mind that the incidence of early syphilis and of fluoroquinolone-resistant *N. gonorrhoeae* have markedly increased in the last several years among men who have sex with men (19).

Bacterial vaginosis, a condition associated with depletion of hydrogen peroxide–producing *Lactobacillus* species and the most common cause of vaginitis among women of reproductive age, is associated with pelvic inflammatory disease, increased risk of acquiring gonorrhea and HIV, and adverse outcomes of pregnancy (20). The prevalence of bacterial vaginosis among lesbians is high, and vaginal colonization with hydrogen peroxide-producing lactobacilli is low, relative to that of heterosexual women matched for age and sexual risk behavior (5,7,21,22).

Bacterial vaginosis prevalence among lesbians in these studies has ranged from 24% to 51%, compared to 21% for heterosexual clients of sexually transmitted disease clinics and 9%–14% for pregnant women. Although bacterial vaginosis is not a classic STI in that a specific microbial precipitant has not been identified, among heterosexual women, report of a new male sex partner and unprotected intercourse are frequently associated (20). Moreover, in early studies of "*Hemophilus vaginalis* vaginitis," Criswell and Gardner transmitted bacterial vaginosis from one

woman to another by transferring vaginal secretions of women with bacterial vaginosis to noninfected women (23). Indeed, bacterial vaginosis is frequently found in both members of monogamous lesbian couples (7,24). In these women, bacterial vaginosis has been associated with sexual behavior that is likely to result in the transfer of vaginal fluid (7). These observations have prompted some authors to propose that sexual transmission of some etiologic factor, as yet undefined, is responsible (24).

Finally, lesbians who are also currently sexually active with men may, in some settings, demonstrate increased sexual risk-taking behavior. Among women attending STD clinics, those who report sex with women in addition to sex with men also had a marked increase in HIV-related risk behavior, including sex with gay or bisexual men, use of injection drugs and crack cocaine, and exchange of sex for drugs or money (17,18). In the 1997 College Alcohol Study, comprised of 14,251 randomly selected U.S. college students, women who reported sex with both men and women were more likely to report multiple sex partners than their peers who had partners of the opposite sex only (25). In addition to STI exposure from male partners, previous or current sex with men has obvious implications for lesbians' reproductive health status. The prevalence of reported lifetime pregnancy among lesbians in the studies that have addressed this issue ranged from 23% to 35% (26–28). Among 392 women in the Seattle Lesbian Health Study, 1 in 4 participants had been pregnant, and >50% had used oral contraceptives (mean duration, 40 months) (28). Sixteen percent of all persons and 63% of those previously pregnant reported having at least one induced abortion. The most common pregnancy outcome for women who became pregnant at age ≤25 years was induced abortion, which occurred in 59% of these pregnancies.

Preventive Healthcare, Including Pap Smear Screening, in Lesbians

Despite the observations that support probable sexual transmission of HPV between women, many lesbians undergo routine Pap smear screening less frequently than national guidelines advise. In the Seattle Lesbian Health Study, 236 (95%) of respondents believed they should receive Pap smears annually or every 2 years after normal smear results, but 90 (36%) provided a reason for not having done so (12). Reasons most commonly cited were lack of insurance, adverse experience at prior Pap smear screening, and a belief they did not need it because they were not sexually active with men. Nine study participants were told (by physicians in all but one case) that they did not need a Pap smear because they were not sexually active with men. Despite high levels of education and income, women with no previous sex with men were less likely to have ever received a pelvic examination, had their first Pap smear at an older age, and had Pap smears less frequently than women who reported previous sex with men. Other investigators have also reported a lower rate of recent pelvic examinations or Pap smears among lesbians (29,30). Among the few nationally representative surveys, the Boston Lesbian Health Project used snowball sampling (participants from the group of interest are asked to refer members of their social or sexual network for consideration for enrollment in the study) to query a national sample of 1,633 lesbians (31). Although the overall screening rates approximated those of the general population, 39% of respondents <20 years and 16% of those 20–29 years had never had a Pap smear, and 29% of those 30–39 years had not had one in >3 years.

One of the few population-based surveys performed with lesbians as the intended audience used a random digit dialing survey to compare the physical and mental health status of 4,135 respondents as a function of self-reported sexual orientation (32). Both lesbians and bisexuals were more likely to report increased rates of poor physical and mental health, as other studies have also noted (33). Reasons for these findings are unclear. Potential barriers to preventive care by lesbians include healthcare providers' lack of knowledge about disease risk and indications for screening; providers' failure to obtain a complete sexual history from lesbians when relevant, or to do so in a sensitive, nonjudgmental manner; patients' lack of economic resources (due to lack of insurance in the absence of domestic partner benefits, unwillingness to disclose sexual orientation to obtain such benefits when they are offered, or lower earnings in households without at least one man); and lesbians' perception of low risk for STI acquisition from female partners and of cervical dysplasia. Many lesbians (53%–72%) do not disclose their sexual behavior to physicians when they seek care, and disclosures may elicit negative reactions (34). Moreover, among 1,086 lesbians surveyed, only 43% of women with a clear risk factor for HIV perceived themselves to be at risk (35). Similar assumptions about HPV acquisition from female partners may place lesbians at risk for delayed detection of cervical cancer by less frequent Pap smear screening or none. Finally, lesbians who do not also have sex with men may not access venues providing hormonal contraception, thus eliminating another routine opportunity for Pap smear screening to be sought or offered.

Conclusions and Future Directions

Available data strongly suggest that HPV, and probably other STIs, are sexually transmitted between women. Thus, recommendations for Pap smear screening among lesbians should not differ from those for heterosexual women, a point that should be clearly communicated in national guidelines and relevant training programs. For

example, no national guidelines for STI or Pap smear screening or treatment mention the existence of lesbians, if even to note that data to direct recommendations are limited or absent (36). Moreover, healthcare providers, particularly those in training, would benefit from education to enhance their skills in taking a thorough, sensitive sexual history from all patients. The recent increases in STI among men who report sex with men but who do not identify themselves as gay also show that simply asking patients their self-defined sexual orientation is not adequate. Assessment of specific sexual risk behaviors and of previous sexual history can provide a more complete tool for assessment and counseling of patients' sexual health status.

From the research perspective, high-risk HPV types and SIL among lesbians support the need for further investigation. Conditions that could contribute to more infrequent Pap smear screening, including perception of low risk, provider behaviors, or economic barriers, should be defined, as should risk for specific STI transmission. Prevalence of common STI, especially *C. trachomatis* infections, should be systematically studied among young women at highest risk for such infections. Beginning to describe the sexual networks in which lesbians participate—particularly as they involve men at potentially high risk for STI, notably HIV—should provide much-needed data into the sexual and social dynamics of a highly diverse population. The intriguing observation of bacterial vaginosis concordance within female sexual partnerships should offer an opportunity to decipher the puzzling etiology of this common condition. This information could not only contribute to advances in understanding the microbiologic and sociologic characteristics of STIs in general, but more immediately, would inform a cogent approach to counseling lesbians and educating healthcare providers about STI-related risk and prevention.

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Gender and Monitoring the Response to HIV/AIDS Pandemic

Paul DeLay*

The mechanisms, techniques, and data sources used to monitor and evaluate global AIDS prevention and treatment services may vary according to gender. The Joint United Nations Programme on HIV/AIDS has been charged with tracking the response to the pandemic by using a set of indicators developed as part of the Declaration of Commitment endorsed at the U.N. General Assembly Special Session on AIDS in 2001. Statistics on prevalence and incidence indicate that the pandemic has increasingly affected women during the past decade. Women's biologic, cultural, economic, and social status can increase their likelihood of becoming infected with HIV.

Since 2000, global financial resources have increased to allow expansion of both prevention and treatment services through a number of new initiatives, such as the Global Fund to Fight AIDS, TB and Malaria; the U.S. President's Emergency Plan for AIDS Relief; and the World Bank MAP program. Programs should be monitored and evaluated to ensure these investments are used to maximum effect. Different types of data should be included when assessing the status of the HIV/AIDS epidemic and effectiveness of the response. Each of these "data streams" provides information to enhance program planning and implementation.

Types of Data

Biologic Surveillance

These types of data include the prevalence of HIV infection in the general adult population and in persons at high risk, as well as the actual estimated number of persons who are infected, who have symptoms of AIDS, and who died of the disease. These data are generally obtained from a combination of sentinel surveillance methods and biologic testing as part of community population surveys.

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Policy Environment

These types of data include establishing policies that increase access to services, protect the rights of vulnerable groups, and provide adequate resources. These data are primarily obtained from a set of discrete tools that include the National Composite Index and the AIDS Programme Effort Index; both tools review legislation, policies, and key interviews of relevant groups, including government officials, clinical providers, and persons affected by or living with HIV/AIDS.

Behavioral Surveillance

These types of data measure levels of risk for HIV transmission and changes in risk levels over time. Major population survey questionnaires, such as demographic health surveys, gather this information, along with targeted behavioral surveillance, such as the Behavioral Sentinel Surveillance Surveys, pioneered by Family Health International.

Resource Flows Data

These types of data include tracking the contributions from external donors (bilateral, World Bank, Global Fund to Fight AIDS, TB and Malaria; and international foundations) as well as national expenditures and "out of pocket" spending from families and persons affected by HIV/AIDS. These data are generally obtained from global resource tracking databases (e.g., Organization for Economic Cooperation and Development) and at the country level from subanalyses of National Health Accounts and through the use of a new tool, National AIDS Accounts.

Tracking Commodities

These types of data provide useful proxy information on program implementation. They are often only available from the donor community that procures these commodities (drugs, condoms, and HIV diagnostic kits) and are rarely routinely collected as part of a country's health information system.

Prevention and Treatment Services

These types of data are generally measured through health information systems. However, because such systems are often inadequate in many developing counties, these data remain poor. Tracking services, for prevention or treatment, also necessitates monitoring the quality of these services. Much of this information can be obtained from health facility surveys, but these surveys are staff- and resource-intensive and are generally not conducted routinely.

Disease and Death Data

These types of data are frequently obtained from vital events registration, including estimated births, deaths, and causes of death. Again, in many developing countries, the collection of this type of information tends to be deficient.

Response Indicators

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has been charged with tracking the response to the pandemic by using a set of indicators developed as part of the Declaration of Commitment, which was endorsed at the U.N. General Assembly Special Session on AIDS in 2001. When these indicators were first measured in 2003, differences in the comprehensiveness and quality of available data became clear. The biologic surveillance data are improving over time, and now the policy environment can be assessed to determine levels of commitment. However, we currently obtain very poor data on commodities, resource flows, and the coverage and quality of prevention and treatment services. This lack of credible data is made worse by the inability to disaggregate these activities by gender.

Biologic Surveillance Data

Until recently, most of this information has been gathered from sentinel surveys of general adult populations and populations at risk. These data are now being complemented by the increasing use of population surveys that include seroprevalence testing. These new data collection methods deepen our understanding of the pandemic. Statistics on prevalence, incidence, and estimated numbers of persons infected with HIV and those with HIV disease have gender implications and point to the increased feminization of the pandemic over the past decade. Almost 60% of HIV-infected persons in sub-Saharan Africa are female. Nearly 20 million HIV-infected persons in the developing world are girls and women (Figure 1). Biologic and behavioral data explain why these different vulnerabilities exist and what sort of interventions could address these different transmission dynamics. Other data indicate that women in sub-Saharan Africa are often infected in their teens while men become infected in their 20s, a 10-year difference.

Policy Environment

A major focus of The U.N. General Assembly Declaration of Commitment is to examine whether countries themselves are creating an environment with a positive and effective response. Are the appropriate policies in place? Is there real commitment by government and civil society to implementing programs that will make a difference? UNAIDS attempts to examine stigma and discrimination by using the National Composite Policy Index (NCI), the AIDS Program Index (API), and a series of media analyses. Globally, funds made available by various sources, HIV/AIDS policies within multinational corporations, and the value of global advocacy efforts are measured. At the national level, funds from national governments, existence of policies to promote programs for risk reduction, and access to care and treatment are measured.

NCI assesses legislation and policy related to national strategic plans, prevention efforts, maintenance of human rights, and provision of care and support. For instance, if a national strategy exists for HIV/AIDS, does it address those at risk in the uniformed services, youth, migrants, and other risk groups? Does the strategy address human rights, particularly access to services for women? However, this approach does not assess the public's awareness of this legislation, how the policy is enforced and implemented, or the quality of these policies. For example, in sub-Saharan Africa, 80% of developing countries have a policy in place to provide antiretroviral therapy, but only 1% of HIV-infected persons in this region actually have access to these lifesaving treatments.

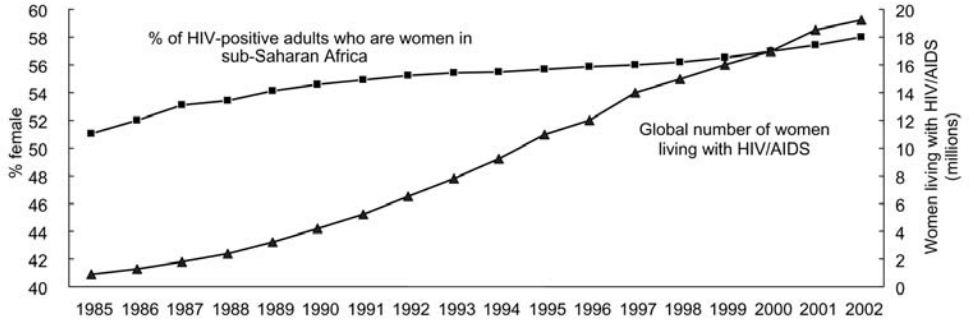

Figure 1. Feminization of HIV/AIDS epidemic, 1985–2002. Source: United Nations Joint Programme on HIV/AIDS, World Health Organization. Estimates; 2002.

In addition to NCI, which quantitatively measures the policy environment, we are also using API, which is a more qualitative, subjective index that examines a range of issues, including stigma, discrimination, and access to services. API is measured by using a Delphi approach. Relevant groups (civil society, health workers, policymakers, government officials, businessmen, religious leaders, persons living with AIDS) are brought together and asked a series of ≈100 standardized questions. This instrument allows us to assess whether policies are actually being implemented and whether they are making a difference. This tool has become increasingly useful to measure subtle and complex changes that occur in a country response, and it is now being applied to other interventions, such as the scope and quality of orphan care, which is difficult to track quantitatively.

One downside to the API is that it does not allow for cross-country comparison. The reason is that citizens' expectations about their government vary widely across countries. Some countries may be assessed poorly because the citizens expect more; however, a country with no policy may do well because the expectations from the public are much lower. However, API is being revised to make some of the responses to the structured interview questions less subjective.

Behavioral Risk Data

Behavioral data fall into three areas, which include data on vulnerability, knowledge and awareness, and risk behavior over time. Women have biologic, cultural, economic, and social vulnerabilities that increase their likelihood of acquiring an infectious disease. They also face hostile justice systems, are exposed to sexual violence, lose inheritance rights and property, lack access to reproductive services, and have few support systems

Analysis of data can lead to a better understanding of inherent vulnerabilities. For example, marriage does not necessarily protect against sexually transmitted infections. Marriage at a very young age can actually increase vulnerability, initiating a young woman into sexual activity earlier than if she were not married. While we believe these findings could be a pathway for future potential interventions, exactly what these programs would look like is being debated.

Figure 2 presents a collection of the knowledge and awareness data that are now being measured in many countries on a more routine basis. Data on the knowledge of how a person becomes infected and how we can protect ourselves are often better disaggregated by gender than many of the other data streams because knowledge assessment surveys are often performed in a same-sex venue. In many ways, girls understand prevention data better than boys. Girls tend to be more accessible to the transfer of information. However, their ability to act on this knowledge is often where the vulnerabilities lie.

The age of first sexual activity can be closely correlated with HIV prevalence (Figure 3). However, the definition of sexual debut can be difficult because much of these data come from retrospective interviews. Persons are asked to remember when their first sex act occurred. The validity of some of these data is questioned, and these methods do not easily permit an assessment of current sexual practices of young persons.

Cross-generational sex is a controversial, but important, area when considering vulnerability. Recently, efforts have been increased to better understand what is happening in this area. While exploitation is a reality, not all persons involved perceive these acts as exploitation. Most young women participate in these relationships to survive. Older men think that they reduce their chance of being infected by being with a younger girl. Addressing these complex and culturally sensitive issues will require innovative thinking.

Violence is another major issue that makes women vulnerable. Data from South Africa indicate that 33% of women are afraid of saying no to sex, 29% have been forced to have sex, and 55% have had sex because their boyfriend insisted (1). In Botswana, the number of reported rapes has increased, but the number of convictions has not (Figure 4).

Tracking Resource Flows

While not traditionally part of monitoring and evaluation, tracking financial resource flows is now considered a

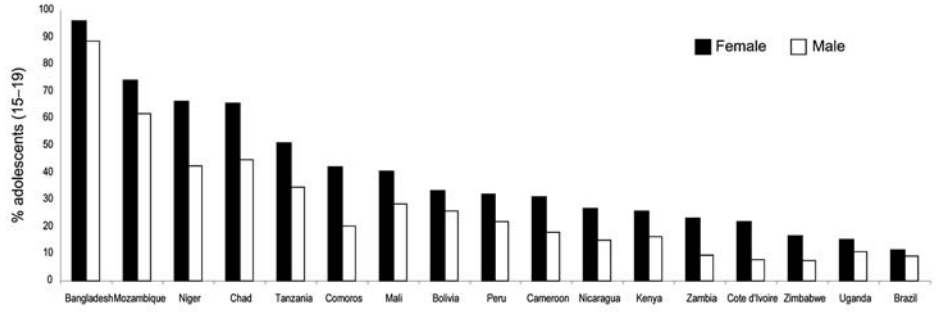

Figure 2. Percentage of adolescents (15–19 years) who do not know how to protect themselves from HIV. Source: Macro International, USA and United Nations Children's Fund, demographic and health surveys.

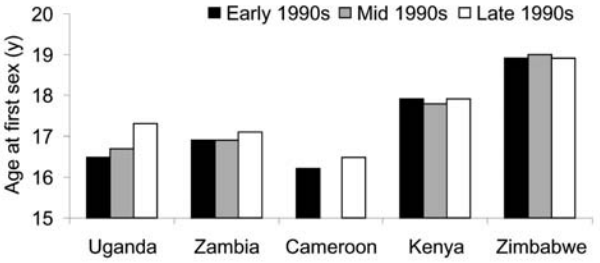

Figure 3. Median age at first sexual intercourse among young women. Source: World Health Organization. HIV/AIDS epidemiologic surveillance update for the WHO Africa region.

key element for monitoring program implementation and effectiveness. How much money comes from the U.S. government or other international donors into a country versus how much comes from the national government itself? Do you see economies of scale as service coverage goes up? Do commodities, such as antiretroviral drugs, become more inexpensive, or as we move from first-line to second-line antiretroviral treatments, will the costs actually go up over time. At a global level, we rely on the Organization for Economic, Cooperation, and Development, which was created by the major industrialized countries to track financial resources and by the Netherlands Interdisciplinary Demographic Institute, which is under contract to UNAIDS to provide information on funding levels from bilateral donors, multilateral organizations, foundations, and the private sector. Resource flows are often tracked at the country level through National Health Accounts and National AIDS Accounts. Figure 5 shows funding levels for AIDS activities in the developing world from various sources.

While spending is increasing, so are unmet needs. The estimated need represented by the top portions of the bar chart (Figure 5) does not include the necessary investments in infrastructure, such as the costs for building more hospitals, clinics, and laboratories, and for training more people. These estimated needs represent what could be spent now with existing infrastructure. The right resources should go to the right places. What should the public sector pay for? What should the private corporate sector pay for? These ratios will change from country to country. We need to examine efficiency of allocations. Assessing equity of allocations is equally important. Is the money actually going to the populations that need it the most? Is it going to a general Information Education Communication campaign, or is it going to the populations at highest risk? Is it staying in the cities or reaching rural settings?

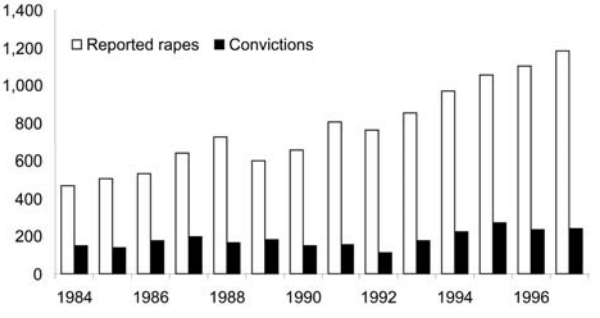

Figure 4. Number of reported rapes and convictions in Botswana. Source: Emang Basadi Women's Association, Botswana, 1998.

Service Delivery and Coverage

To examine services and coverage, we use key informant coverage surveys, health facility surveys, and donor data. In the UNAIDS 2003 Progress Report on the Global Response to the HIV/AIDS Epidemic, the available data on the delivery of preventive and treatment services demonstrated a lack of access. Only 1 in 100 pregnant women receives services to prevent mother-to-child transmission of HIV. One in 100 eligible HIV-infected persons (men and women) has access to antiretroviral therapy. One in 10 has access to testing for HIV infection. One in four has access to basic information on AIDS and protection against AIDS. Much of these data cannot currently be disaggregated by gender. When we look at antiretroviral therapy, ≈400,000 persons in the developing world are being treated, of which ≈80,000 are in sub-Saharan Africa, but the ratio of women to men receiving these services is difficult to break down.

Overall Challenges

We face a number of challenges in containing the AIDS pandemic and increasing prevention and treatment programs, particularly as they relate to gender. Setting standards and targets for equity of access and then monitoring progress will be critical. For example, UNAIDS advocates that of the 3 million infected persons who should be started on antiretroviral therapy by the end of 2005, an appropriate number should be women, depending on the ratio of infected men to women in that specific country.

Measuring sectorwide effects of these new resources will be a major issue. If a massive investment in infrastructure is focused on the three major infectious diseases (AIDS, tuberculosis, and malaria), will the health sector be positively affected as a whole or will we see staff, commodities, and resources diverted from other areas of public health, such as immunization of children or treatment of childhood diarrhea? How are we going to measure this?

A new initiative, the Global Coalition on Women and AIDS, was launched February 2004 by UNAIDS and other partners. The coalition focuses on selected key areas: preventing HIV infection in girls and women, reducing violence against women, protecting property and inheritance

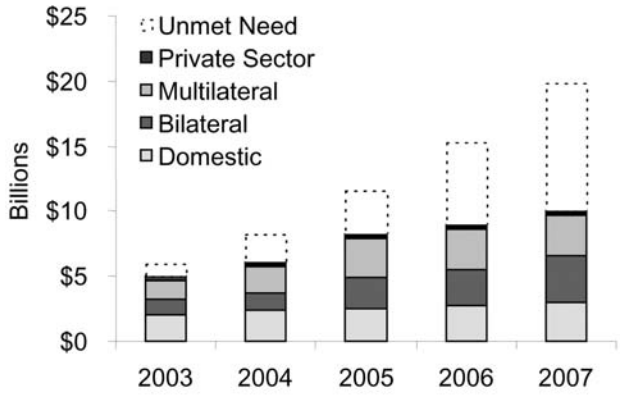

Figure 5. Projected International HIV/AIDS Resource Need and Funding Availability, 2002–2005. Source: United Nations Joint Programme on HIV/AIDS. Report on the state of HIV/AIDS financing; 2003.

rights, ensuring equal access by women and girls to care and treatment, and supporting efforts for universal education for girls. We need to find ways to accurately measure progress in all these areas, while recognizing that quantitative methods may not be the most appropriate way to get a true picture of progress or lack thereof.

We are making progress in monitoring and evaluating prevention measures, but we have a long way to go. As we collect appropriate biologic, policy, behavioral, and service coverage data, patterns of gender dynamics and inequities begin to emerge. We must use this information to address these inequities.

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Nurses' Working Conditions: Implications for Infectious Disease

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Staffing patterns and nurses' working conditions are risk factors for healthcare-associated infections as well as occupational injuries and infections. Staffing shortages, especially of nurses, have been identified as one of the major factors expected to constrain hospitals' ability to deal with future outbreaks of emerging infections. These problems are compounded by a global nursing shortage. Understanding and improving nurses' working conditions can potentially decrease the incidence of many infectious diseases. Relevant research is reviewed, and policy options are discussed.

The Institute of Medicine's report, To Err is Human, which spotlighted the problem of patient safety, reported that tens of thousands of Americans die each year as a result of human error in the delivery of health care (1). Authors of a more recent Institute of Medicine report, Keeping Patients Safe, Transforming the Work Environment of Nurses, concluded that nursing is inseparably linked to patient safety and emphasized that poor working conditions for nurses and inadequate nurse staffing levels increase the risk for errors (2). Nurse working conditions are related to patients' risk of healthcare-associated infections and occupational injuries and infections among staff (3). We discuss the nurse workforce, review research examining nursing as it relates to infectious disease, identify gaps in the literature, and discuss potential policy options. Although our focus is on the nursing workforce in the United States, international trends and comparisons are also discussed.

The Nursing Workforce

Nearly 3 million registered nurses (RNs) work in the United States. Ninety-five percent of these nurses are women, as are most of the 700,000 licensed practical nurses and >2 million unlicensed nurse assistants. Internationally, occupational distributions are similar.

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More than 1 million RNs work in hospitals, which makes nursing the largest hospital workforce. In 60% of U.S. hospitals, vacancy rates for RNs have increased since 1999; 14% of hospitals now report a severe nurse shortage (i.e., >20% of positions vacant). The American Hospital Association has reported that hospitals have up to 168,000 vacant positions; 126,000 (75%) of the available positions in these hospitals are for RNs (4). The current nursing shortage is related to an aging workforce, problems with retaining licensed personnel, and difficulty recruiting young people into the nursing workforce. The demand for RNs is projected to grow by 22% by 2008, and unless market corrections are made, the nursing shortage may reach 800,000 vacant positions by 2020 (5). Recent reports document that the nursing shortage is a severe and growing global problem (4).

Historically, the turnover rate among nurses is more than double that for other professionals of comparable education and sex (6). Recent estimates in U.S. hospitals of RN turnover and intention to quit have ranged from 17% to 36% (6,7), figures that compare to an overall turnover rate of 2.2% for those employed in health services and social services and 1.2% for those employed in educational services. In an investigation of the effects of various nurse working conditions in intensive care units, researchers found >17% of RNs indicated their intentions to quit within 1 year (P.W. Stone, unpub. data). This finding was disconcerting because this national U.S. sample of 2,324 RNs was highly qualified; their average experience in health care was 15.6 years (SD = 9.20), and their average tenure in their current position was 8.0 years (SD = 7.50). Of those intending to leave, 72% expressed poor working conditions as the reason. In an American Hospital Association–sponsored study, researchers estimated the cost of replacing one RN to be $30,000–$64,000 (4).

To cover patient census fluctuations and unplanned absences and to fill vacant positions caused by this nursing shortage, many healthcare facilities have increased nurses' patient loads or expanded the use of nonpermanent staff, such as float pool and agency nurses (4). Concerns have been voiced that reliance on agency nursing services

elevates hospital costs, increases the fragmentation of health care, and discourages longer term proactive solutions to staffing shortages that would improve the morale of the permanent staff as well as the quality of patient care services (8). Extended work shifts and overtime for nurses have also escalated; however, nurses report making more errors when working shifts >12 hours, working overtime, or working >40 hours per week (9).

To increase the overall supply of nurses, many countries are increasingly relying on international recruitment and migration (10). The percentage of foreign-trained nurses in the United States is 4%, compared to 8% in the United Kingdom and 23% in New Zealand (11). However, the actual number of foreign-trained nurses in the United States is 90,000, which compares to 42,000 in the United Kingdom (12). In 2002, for the first time more foreign-trained nurses (n = 16,155) were newly registered in Britain than were those who had been educated within the country (n = 14,538). Many concerns exist about clinical competencies, cultural sensitivity, and ethics of the practice of importing nurses (13). While international recruitment can be a solution in one country, it can create additional shortages in others.

Nursing and Healthcare-associated Infections

A recent evidence-based practice report sponsored by the Agency for Healthcare Quality and Research concluded that a relationship exists between lower levels of nurse staffing and higher incidence of adverse patient outcomes (14). Nurses' working conditions have been associated with medication errors and falls, increased deaths, and spread of infection (15–30) (Table). RN staffing levels have been associated with the spread of disease during outbreaks (17,22,23,25,28). However, increasing nurse-to-patient ratios alone is not adequate; more complex staffing issues appear to be at work. Many studies have found that

Table. Summary of studies on nurse staffing and healthcare-associated infections[a]

Investigator	Sample	Findings
Outbreak investigations		
Anderson et al. (17)	36-bed neonatal ICU; 8 cases	During MRSA outbreak, 42% staff untrained, up to 62% from outside facility
Archibald et al. (28)	1 pediatric ICU; 43 patients	Decrease 2 infections/1,000 patient days for each unit increase in RN h: patient-day ratio[b]
Fridkin et al. (25)	230-bed VA center; 170 patients	Patient-nurse ratio increased during BSI outbreak[c]
Harbarth et al. (22)	15-bed neonatal ICU; 8 cases	*Enterobacter cloacae* outbreak terminated after decrease workload
Vicca (23)	1 adult unit; 50 cases	MRSA[b] cases associated with increase workload, decrease RN-patient ratio
Prospective studies		
Alonso-Echanove et al. (16)	8 ICUs; 4,535 patients	Float RNs >60% central venous catheter days increased risk for BSI[d]
Haley et al. (26)	85-bed neonatal ICU; 76 infants	MRSA infections increased within 1 month of worsening workload[c]
Robert et al. (21)	20-bed surgical ICU; 28 cases	BSI associated with lower regular nurse-patient and higher pooled staff-patient ratios[b]
Retrospective studies		
Amaravadi et al. (19)	32 hospitals; 353 patients	Night nurse-patient ratio <1:2 associated with pneumonia[c] and BSI[c]
Arnow et al. (27)	1 burn unit; 147 patients	New cases MRSA[b] paralleled number of overtime h and number of shifts by outside staff
Knauf et al. (30)	502 hospitals	Pneumonia,[c] postoperative infection,[c] UTI[c] associated with low RN h and skill mix
Kovner et al. (15)	530–570 hospitals; 10 states	Increase nurse h per adjusted patient day associated with decreased pneumonia[c]
Kovner & Gergen (24)	589 hospitals; 1,993 patients	Increase RN FTEs associated with decreased UTI[b] and pneumonia[b]
Lichtig et al. (20)	1,575 hospitals	Pneumonia,[b] postoperative infection,[b] UTI[b] associated with low RN skill mix
Needleman et al. (29)	799 hospitals; 6,180,628 patients	Higher proportion RN h, higher RN h per day resulted in decreased UTI[b]
Stegenga et al. (18)	44-bed pediatric unit; 2,929 admissions	<10.5 nurse h per patient day resulted in increased gastrointestinal infections[c]

[a]HAI, healthcare-associated infections; RN, registered nurse; MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; UTI, urinary tract infection; VA, Veterans Administration; ICU, intensive care unit; FTE, full-time equivalent.
[b]Significant at $\leq$0.005.
[c]Significant at $\leq$0.05.
[d]Significant at 0.01.

the times of higher ratios of "pool staff" (i.e., nursing staff who were members of the hospital pool service or agency nurses) to "regular staff" (i.e., nurses permanently assigned to the unit) were independently associated with healthcare-associated infections (16,17,21,27). The skill mix of the staff, that is, the ratio of RNs to total nursing personnel (RNs plus nurses' aides), is also related to healthcare-associated infections; increased RN skill mix decreases the incidence of healthcare-associated infections (20,29,30). In a recent comprehensive review of the literature, the authors concluded that evidence of the relationship between nurses' working environment and patient safety outcomes, including healthcare-associated infections is growing. They also concluded that stability, skill mix, and experience of the nurse workforce in specific settings are emerging as important factors in that relationship (31).

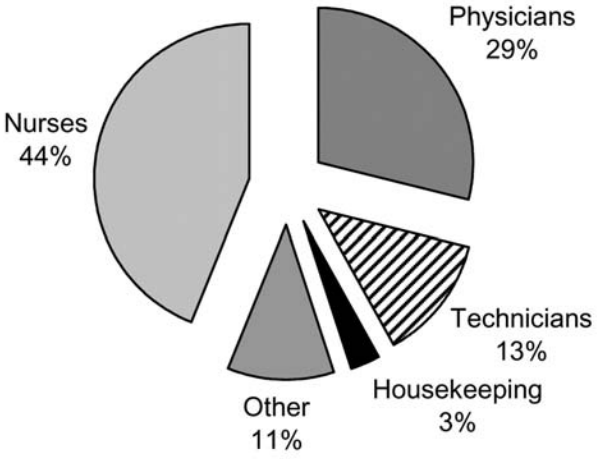

Figure. Blood and body fluids' exposure by personnel category. Source: National Institute for Occupational Safety and Health (34).

Nurses' Work and Occupational Exposure to Infectious Disease

All healthcare workers face a wide range of hazards on the job, including blood and body fluid exposure as well as musculoskeletal injuries related to ergonomic hazards from lifting and repetitive tasks; nursing personnel often experience these hazards most frequently (32). In 2001, U.S. hospitals reported 293,600 nonfatal occupational injuries and illnesses among their personnel. Among the eight private U.S. industries with ≥100,000 injuries and illnesses annually, the number of cases of nonfatal injury or illness in hospitals is the second highest; and the incidence rate of injuries and illnesses per 100 fulltime workers employed in nursing and personal care facilities is 13.5; by contrast, the national average is 1.8. In 2001, nursing aides and orderlies reported the highest number of occupational injuries that resulted in days away from work of any service industry (70,300); RNs had the second highest number (24,400) (33).

Work-acquired infectious diseases are among the risks all healthcare workers face; and bloodborne pathogens figure prominently among these. Occupational exposure to blood and body fluids is well documented among healthcare workers. Annual exposure prevalence rates range from <10% to 44%, depending on the occupational subgroup (34). Every year, approximately 600,000–800,000 occupational needlestick injuries occur in the United States (34). In a study of 60 U.S. hospitals in a 4-year period, nurses were the most likely to experience a blood or body fluid exposure (Figure) (34). Most exposures involve percutaneous injuries (e.g., needlesticks), although mucocutaneous (e.g., spray or splashes to the eyes or mouth) and direct contact of infected blood with nonintact skin are also routes of exposure. These potential infections, like healthcare-associated infections, also appear to be tied to nurses' working conditions. In a cross-sectional study of >1,500 nurses employed on 40 units in 20 hospitals, poor organizational climate and high workloads were associated with 50% to 200% increases in the likelihood of needlestick injuries and near-misses among hospital nurses (3).

Emerging infectious diseases and outbreaks of recognized contagious illnesses have highlighted other concerns about the safety of healthcare workers. For example, much of the worldwide severe acute respiratory syndrome (SARS) outbreak was hospital-based, and healthcare workers made up a large proportion of cases, accounting for 37% to 63% of suspected SARS patients in highly affected countries (35). In many countries, nurses were the largest single group affected by SARS (36). During the Toronto outbreak, patient care activities commonly conducted by critical care nurses, such as manipulating oxygen masks and suctioning infected patients, were significantly associated with SARS infection (37). In the event of an influenza pandemic, healthcare workers would be susceptible. During an outbreak of parainfluenza in a intermediate care nursery, 16 (25%) of 65 staff members reported symptoms of respiratory illness (38). These threats to safety of the nurse and other essential healthcare workers are of concern for many reasons.

First, a trained, qualified healthcare workforce is necessary to respond and care for the public in the event of an outbreak. Staffing issues and hospital organization problems are believed to have complicated the containment of the SARS crisis in Toronto. Staffing shortages, especially of nurses, have been identified as one of the major factors expected to constrain hospitals' ability to deal with possible future threats (4). Without adequate numbers of trained hospital employees to implement effective infection control procedures, such as hand hygiene and proper isolation procedures, emergency departments and hospital wards

can easily become the venues where the spread of epidemics occurs.

Second, the perception of unsafe working conditions both for the patient and the worker may actually hinder recruitment and retention of qualified staff. In a American Nurses Association survey of RNs (N = 7,353), 88% of respondents reported health and safety concerns related to work, 75% felt the quality of nursing care had declined in their work setting in the past 2 years, and 92% of those respondents related these concerns to inadequate staffing. Furthermore, >70% of respondents indicated concerns about the acute and chronic effects of work stress and overwork, concerns about a disabling back injury (60%), and fear of contracting HIV or hepatitis from a needlestick injury (45%). Nurses reported that these health and safety concerns influence their decision to continue working in the field of nursing and the kind of nursing work they choose to perform. Because of these concerns, nearly 55% of the nurses surveyed would not recommend the nursing profession as a career for their children or friends. Although the results of this survey may not be generalizable to all nursing personnel because of the nonprobability sampling method and inclusion of only RNs, the results suggest that concern over safety may be contributing to hospital personnel shortages and hindering recruitment efforts. Dissatisfaction, burnout, and concerns about quality of care are reportedly common among hospital nurses in five other industrialized countries (39).

Gaps in Current Knowledge

Barring unprecedented growth in the nursing workforce or unforeseen new forces in health care that intervene to reduce burden of care in society, the numbers of nurses will not keep pace with the demand for services. In the coming decades, we face the prospect of fewer professionals and more unlicensed workers in the healthcare workforce. Decisions will have to be made about how hospitals will safely adapt to this situation. At this time, little evidence exists on what constitutes a safe and efficient labor force mix. Therefore, the general impact of nurse working conditions needs to be examined. First, longitudinal studies that track change in infection rates and other untoward incidents over time, under different working conditions, and with different staffing models are essential. Second, researchers need to study how the actual care received by patients varies under different staffing conditions at the bedside so that a better understanding of the impact of work environments at the point of care can be gained. Finally, since costs of care increase when patients have adverse outcomes (40) and nurses' working conditions affect outcomes, better working conditions could arguably save the healthcare system money. However, the cost-benefit ratio is not known and economic analyses, which include costs related to training, recruitment, and retention, need to be conducted.

Implications for Policy

Policy solutions for nurse staffing fall into two general categories: 1) incentives and funding for various parties to increase the supply of nurses and 2) employer and hospital regulatory approaches. Although scholarships, loan forgiveness schemes, and funding of new nursing school student slots may be helpful, these policies are unlikely to overcome the long-standing, complex nature of the difficulties in recruiting sufficient newcomers to the nursing profession and then retaining a qualified workforce.

In the United States, regulatory approaches by the states have included prohibiting mandatory overtime for nurses (nine states with regulations), holding hospitals accountable for developing and implementing valid staffing plans (seven states), and setting minimum staffing ratios (one state). Regulating minimum nurse-patient ratios has received much attention, despite critiques from the hospital industry that insufficient data exist to credibly set minimum safe staffing levels. California was the first state to implement hospitalwide minimum nurse-patient ratios. The effects of this regulation need to be carefully examined. Although nursing services are positively correlated with patient outcomes, controversy exists over what constitutes an optimal staffing ratio, and little empirical evidence is available on which to base these decisions.

Staffing levels for bedside nurses are not the only critical resource involved in decreasing risks for healthcare-associated infections, occupational injuries, and infections. Also important is determining the critical mass of infection control and occupational health professionals needed for surveillance, identification of departures from sound practices, and ongoing education of healthcare workers. Policies aimed at ensuring the availability of training programs on all aspects of patient and worker safety are needed, as is the availability of appropriate supplies to prevent unnecessary infections among patients and nurses.

Conclusions

Nursing is a predominately female occupation in which the working conditions are often poor. Such conditions contribute to recruitment and retention problems. Together with demographic changes, the result is a shortage of qualified nurses. Mounting evidence demonstrates that the lack of an adequate supply of qualified nurses is a global public safety issue that may require a multipronged policy approach. Monitoring and improving the working conditions of nurses are likely to improve the quality of health care by decreasing the incidence of many infectious diseases, assisting in retaining qualified nurses, and encouraging men and women to enter the profession. Further

research is needed to understand how best to protect the patient as well as the healthcare worker. Changes in the workforce will have implications for infectious disease, infection control, and occupational health professionals with a need for much more thorough training of nonprofessionals in critical practices.

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Vaccines for Women Age 50 and Older

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For older populations, most of whom are women, preventing illnesses and deaths through the use of vaccines is a leading public health challenge. Our understanding about how age and sex affect the immune system is limited, and basic and translational research aimed at improving vaccines and immune responses of older persons is needed. In the meantime, fully implementing current vaccine recommendations, particularly those for influenza and pneumococcal vaccines, can save thousands of lives and prevent illnesses in persons >50 years of age.

In the United States, the elderly are more likely to die of a vaccine-preventable disease. Adult deaths from influenza (≈36,000/y) (1,2), invasive pneumococcal disease (≈9,000/y) (3), and hepatitis B (≈5,000/y) (4) exceed vaccine-preventable deaths among children (≈50/y) by a ratio of ≈1,000:1. For each of these diseases, case-fatality rates rise with increasing age. This disparity can be addressed through adult vaccination programs, which are cost-effective and life-saving. Women constitute most of the adult U.S. population ≥50 years of age (60% of those 75 years of age and 70% of those 85 years of age).

The immune system does not function as well with advancing age (5). For example, T-cell functions diminish with age, as evidenced by the increased prevalence of anergy to mycobacterial and fungal skin-test antigens and the increased frequency and severity of herpes zoster infection with age. B-cell function diminishes, as seen with the lessened humoral response (immunoglobulin [Ig] M, IgG, and IgA) to certain vaccines (e.g., hepatitis B, influenza, pneumococcal vaccine), and the protective efficacy of these vaccines also decreases as recipients age (6,7).

Differences in Immunologic Response by Sex

Very little is known about differences in the immunologic response to vaccines or their protective efficacy, according to sex and age. Higher antibody responses have been noted in women after hepatitis B vaccination (8,9). Trials are being completed to evaluate the effect of high dose varicella vaccine in reducing the high rates of herpes zoster and postherpetic neuralgia (10,11) in elderly. Some studies suggest that these problems preferentially involve older women. However, none of the differences reported between sexes are of a magnitude that affects any of the current vaccine recommendations.

The 2003–2004 Recommended Adult Immunization Schedule by Age Group, United States (12) (available from http://www.cdc.gov/nip/recs/adult-schedule.htm) covers the vaccines most commonly used for specific age brackets (Figure). We discuss the vaccines universally recommended for adults ≥50 years of age and selected vaccines for international travelers. Vaccine recommendations for special medical conditions (e.g., asplenia, pregnancy, diabetes, immunodeficiency, HIV infection, hepatitis exposures) may be found elsewhere (12).

Universal Vaccines for Persons ≥50 Years of Age

Influenza

In an average year in the United States, influenza causes ≈36,000 deaths, 114,000 hospitalizations, 25 million physician visits, and an additional 30–60 million milder infections (1). Death and severity of illness are correlated with increasing age and underlying conditions. Persons at high risk for influenza complications include persons ≥65 years of age, residents of chronic-care facilities, and persons with chronic medical conditions, such as pulmonary, metabolic, or cardiovascular disorders; renal dysfunction; immunocompromised conditions; and splenic absence or dysfunction. Because ≈30% of the U.S. population 50–64 years of age have one or more conditions that warrant influenza vaccination (1) and because age-based recommendations are easier to implement, 50 years of age has now been established as the time for beginning the universal annual influenza vaccination (13).

The only influenza vaccine currently licensed for persons ≥50 years of age is the killed trivalent influenza vaccine (TIV), which is annually constituted to contain the two type A strains and one type B strain thought most

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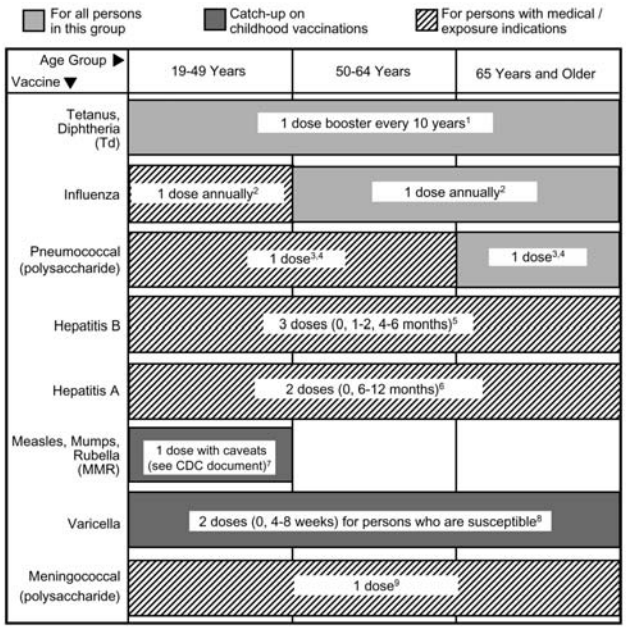

Figure. Recommended Adult Immunization Schedule, United States, 2003-2004 (12). This schedule indicates the recommended age groups for routine administration of currently licensed vaccines for persons >19 years of age. See http://www.cdc.gov/nip/recs/adult-schedule.htm for complete documentation of the numbered footnotes.

likely to circulate in the next influenza season. The vaccine usually becomes available in late September and should be administered annually, ideally from September to November. If the circulating and vaccine strains are well matched, 70%–90% of healthy recipients <65 years of age will be protected against influenza. In elderly and immunocompromised recipients, disease prevention rates are lower because of decreased immune response, but the vaccine is still effective in reducing the severity of illness. In elderly persons living in nursing homes, influenza vaccine can be 50%–60% effective in preventing hospitalization and pneumonia and 80% effective in preventing influenza-related deaths (14–16). Substantial reductions of cardiac events and cerebrovascular disease, as well as pneumonia, among influenza vaccine recipients ≥65 years of age have been reported from a large study in Minnesota (17). If this finding is confirmed, it would be an added benefit of influenza vaccination in elderly populations.

Current rates of influenza vaccination by population group are shown in the Table (1). Although the rates in nursing home residents (83%) are approaching the goal (90%) set by the Healthy People 2010 initiative, the overall rates for the elderly have been stalled at 65% to 67% for the past 3 years and less that one third of persons at high risk in younger age groups have been vaccinated. Fully implementing the current influenza vaccine recommendations would prevent many illnesses and deaths annually, particularly in the elderly, and is a potentially cost-saving public health challenge.

Influenza vaccination of healthcare workers has been a long-standing recommendation for prevention of nosocomial spread of influenza, especially to persons at high risk. Vaccinating healthcare workers in nursing homes has been reported to reduce disease among the residents (18,19); therefore, the overall rate (36%) of vaccination among healthcare workers needs to be increased.

A trivalent, live, attenuated, cold-adapted influenza vaccine (LAIV-T) has been licensed for use in persons 5–49 years of age (1,20). The vaccine is administered by intranasal spray and induces local mucosal immunity as well as systemic immunity. This vaccine appears to provide protection similar to the TIV vaccine and may be superior in years when the vaccine strains do not closely match the circulating virus. LAIV-T requires special cold storage and is more expensive than TIV. At the time of licensure, not enough data regarding its use in elderly persons were presented, and approval for adult use was granted only up to 50 years of age. Studies in older adults are in progress.

The addition of neuraminidase inhibitors (oseltamivir and zanamivir) to the arsenal of chemoprophylactic and therapeutic drugs for influenza poses further options, especially for the elderly, who generally respond less well to vaccines. While previously available drugs, amantadine and rimantadine, have similar efficacy against influenza A and are less expensive, the newer drugs have fewer serious side effects and provide protection against influenza B as well. Data are limited and inconclusive concerning the effectiveness of these drugs for preventing or treating serious complications of influenza.

Questions remain about how best to prevent or modify influenza in the elderly. Should a vaccine with increased antigen dosage or different adjuvants be developed in the hope of improving the antibody levels in older persons? Would a vaccination schedule of twice per season, e.g., October/November and January/February, give more sustained protection to the elderly? Because the immunologic response diminishes with age, should those >80 years of age also receive antiviral chemoprophylaxis during influenza outbreaks? Should antiinfluenza drugs be added to the empiric initial treatment of patients hospitalized for community-acquired pneumonia during the influenza season?

Pneumococcal Disease

The incidence of and deaths from invasive pneumococcal disease rise sharply among adults after 50 years of age (3). Invasive pneumococcal diseases, mainly bacteremia and meningitis, cause ≈9,000 deaths per year in the United States, with case-fatality rates that exceed 50% in the eld-

Table. Influenza vaccination rates by population group[a]

Population group	Vaccinated (%)	By 2010 (%)[b]
Persons ≥65 y	67[c]	90
Nursing home patient	83	90
Persons at high-risk 18–64 y	29	60
Healthcare workers	36	60

[a]Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep. 2003;52(RR-8).
[b]Healthy People 2010 goals.
[c]Vaccination rates for all components of the over-65 age group in 2001 to 2002 were 70% for non-Hispanic whites, 47% for Hispanics, and 52% for non-Hispanic blacks.

erly. Estimates of pneumococcal pneumonia vary from 500,000 cases per year (3,21) to 106,000–175,000 cases per year (22), with case-fatality rates of 5% to 7% among the hospitalized elderly. Pneumococcal disease rates are substantially elevated in certain minority populations, including African-Americans, Alaska natives, and Native Americans.

The pneumococcal polysaccharide vaccine (PPV), which is available for use in adults, consists of purified capsular polysaccharide from the 23 serotypes of pneumococcus, which account for approximately 85%–90% of cases of invasive pneumococcal disease. Overall, this vaccine is ≈60% effective in preventing invasive pneumococcal disease caused by serotypes included in the vaccine but is less effective in the elderly (23). The vaccine has not demonstrated consistent benefit in preventing pneumococcal pneumonia (23–25).

The PPV vaccine is recommended for all adults ≥65 years (12) and for younger adults with chronic medical conditions, including diabetes, heart disease, chronic pulmonary disease (excluding asthma), chronic liver disease (including alcoholism), renal disease, asplenia or splenic dysfunction, HIV infection, and immunodeficiency states (12).

Recent surveys indicate that 66% of persons ≥65 years of age have received one or more PPV vaccinations (26). However, vaccination rates are lower for African-Americans and other minority groups and for younger adults with medical conditions that place them at higher risk for invasive pneumococcal disease. This situation indicates a major preventive medicine opportunity through full implementation of the current recommendations for PPV use. The antibody levels and protective efficacy provided by PPV vaccination gradually wane. Because PPV stimulates B-cells but does not induce T-cell memory, revaccination does not produce an anamnestic response. However, it usually elicits a rise in antibody that approximates the response to the initial vaccination (27).

In the absence of studies of the protective efficacy after revaccination and insufficient safety studies by age, advisory committees have been reluctant to issue firm directives. To date, routine revaccination is not recommended for immunocompetent persons who were first vaccinated ≥65 years of age. However, for persons who were first vaccinated before 65 years of age for reason of increased risk, a single revaccination is recommended (12). In the absence of data, some practicing physicians, given the overall good safety profile and low cost of PPV, have chosen to revaccinate elderly patients at 5- to 10-year intervals as a prudent response to the increasing rates of pneumococcal disease and deaths with age.

Additional questions about PPV recommendations exist. Should the vaccine indications be broadened to include those who smoke cigarettes, now shown to be a major risk factor for invasive pneumococcal disease, (28) and minority groups who have 2–10 times more invasive pneumococcal disease than that of the general population? Should the age for universal vaccination of adults be lowered to 50 years of age (29,30) on the basis of the observations that ≈30% of adults 50–64 years of age have risk factors for which PPV is indicated (13,29)? Approximately 18% of the U.S population is made up of minority groups who have high rates of pneumococcal disease, and approximately one quarter of Americans 50–64 years of age smoke cigarettes. An added advantage to lowering the age of universal PPV vaccination to 50 years of age would be the "harmonization" of the adult pneumococcal vaccination schedule with the recommendations for influenza vaccine (30), thereby simplifying the system and hopefully improving the poor implementation rates of condition-based recommendations.

Finally, the development of a seven-valent pneumococcal conjugate vaccine for infants and young children has been a major advance that provides >90% protection against invasive pneumococcal disease in young children. Since young children are an important reservoir of pneumococcal carriage and spread it to others, vaccinating young children has provided a beneficial herd immunity that results in substantial reductions of pneumococcal disease in other children and adults (31). Developing a pneumococcal conjugate vaccine suitable for adults has been difficult.

Tetanus-Diphtheria (Td) Toxoid Boosters

Tetanus toxoid and diphtheria toxoid are excellent immunogens. The primary vaccination series in childhood provides high-level protection and induces long-lasting immunologic memory, as evidenced by an anamnestic antibody response to Td after intervals of ≥30 years. High levels of primary vaccination and appropriate wound care (including Td boosters) are the cornerstones of tetanus prevention in the United States. The current recommendation that all adults in the United States receive Td boosters every 10 years has been poorly implemented, as evidenced by serosurveys showing that most adults ≥50 years of age lack protective levels of antibodies to either tetanus toxoid, diphtheria toxoid, or both (32). Despite this high level of

serosusceptibility, tetanus (≈30 cases/y) and diphtheria (0–3 cases/y) are rare diseases and almost always occur in persons who never completed the full schedule of childhood vaccinations. Cost and benefit studies favor a policy of a single mid-life Td booster for persons who have completed the full pediatric series (33), and several advisory groups have recommended a booster at 50 years of age as an alternative to the current standard of decennial boosters (12,34). Consideration of reducing the frequency of Td boosters will be complicated by the proposed addition of the acellular pertussis vaccine to the adult Td formulation, as it is more costly and induces a shorter duration of antibody response than Td.

Vaccines for Travelers >50 Years of Age

The increasing participation of older people in international travel raises an additional set of vaccination issues. Influenza and pneumococcal vaccinations should not be overlooked for travelers, especially during the different winter season in the Southern Hemisphere. Similarly, the crowding of people from many parts of the world on cruise ships or other international gatherings, is a setting in which influenza and other seasonal viruses may occur out of season. Hepatitis A vaccine is indicated for all travelers to areas of the world where sanitation or water safety are in question. Although approximately one half the U.S. population >50 years of age has serologic evidence of immunity to hepatitis A because of previous hepatitis A exposure, the pragmatic policy is to give hepatitis A vaccine rather than to serologically screen and vaccinate only the immunosusceptible persons. The vaccine is safe and highly protective when given preexposure and may have benefit when administered early in the postexposure setting. Two doses spaced ≥6 months apart are recommended, although serologic and epidemiologic data suggest that one dose may provide long-term protection. No data are available to indicate the duration of protection in the elderly. For persons who also require hepatitis B vaccination, a combined hepatitis A- hepatitis B vaccine (Twinrix) provides a convenient three-dose method of vaccination. Hepatitis B vaccine is indicated for persons planning long-term travel (generally >6 weeks) to areas of high hepatitis B prevalence or who anticipate parenteral exposure (dental procedures, needle exposure, blood products) or sexual exposure to hepatitis B virus. The standard three-dose schedule is 0, 1, and 6 months, although an accelerated schedule of 0, 1, and 4 weeks offers good short-term protection but requires a fourth dose at 1 year. The duration of protection is not well defined but appears to exceed the duration of the antibody response; therefore, no firm recommendation exists regarding booster doses. However, the immune response to hepatitis B vaccine diminishes sharply with age and for older persons. For older persons with continual or repeated exposures to hepatitis B, measuring antibody levels and considering boosters for those with low levels are advisable. Yellow fever vaccine, a live, attenuated viral vaccine, is indicated for travelers to disease-endemic areas of South America and sub-Saharan Africa, and several countries require proof of vaccination as a condition of entry. Cases of yellow fever among U.S. travelers have been few but have increased in the last decade, and some deaths have occurred. On the other hand, recent reports have described the rare occurrence of a systemic illness mimicking yellow fever after yellow fever vaccine administration to elderly persons (35). Therefore, the vaccine should not be administered to persons (especially the elderly) who are not traveling to yellow fever–endemic areas. Recommendations for the other travel related vaccines (meningococcal, typhoid fever, polio, rabies, and Japanese encephalitis) are the same for all adult age groups and are fully described in Health Information for International Travelers (36).

Future Developments

Because increasing age is associated with increasing rates of herpes zoster and post-herpetic neuralgia, studies are under way to evaluate the administration of high-dose varicella vaccine to persons ≥60 years of age in an effort to boost antivaricella antibodies and reduce the late complications of varicella. Several promising vaccines important to women are in development to prevent cervical cancer (human papillomavirus vaccine), sexually transmitted diseases, and transmission of pathogens (e.g., group B streptococcus, cytomegalovirus) from pregnant women to their newborns, but these vaccines are intended for younger populations and will not be important vaccines for persons ≥50 years of age. The generic problems of lessened vaccine response and efficacy with advanced age call for increased research regarding the immune response in the elderly. Approaches that appear promising include developing age- and sex-specific adjuvants, considering different antigen doses and vaccination schedules that offer the possibility of improving the immunologic response, and vaccines to boost T-cell and phagocytic host defenses. Advances in genetics will facilitate the identification of subpopulations with unique vaccine responses. Also, the ability to genetically engineer vaccines with higher antigen concentrations and the capacity to combine a variety of antigens offer the promise of broader protection with simplified vaccine schedules.

Conclusion

Preventing illnesses and deaths in older populations from diseases that are preventable through vaccines is a leading public health challenge. Our understanding of the effects of age and sex on the immune system is limited.

Fully implementing vaccine recommendations, particularly for influenza and pneumococcal vaccines, offers the immediate prospect of saving thousands of lives and reducing major illnesses among persons ≥50 years of age.

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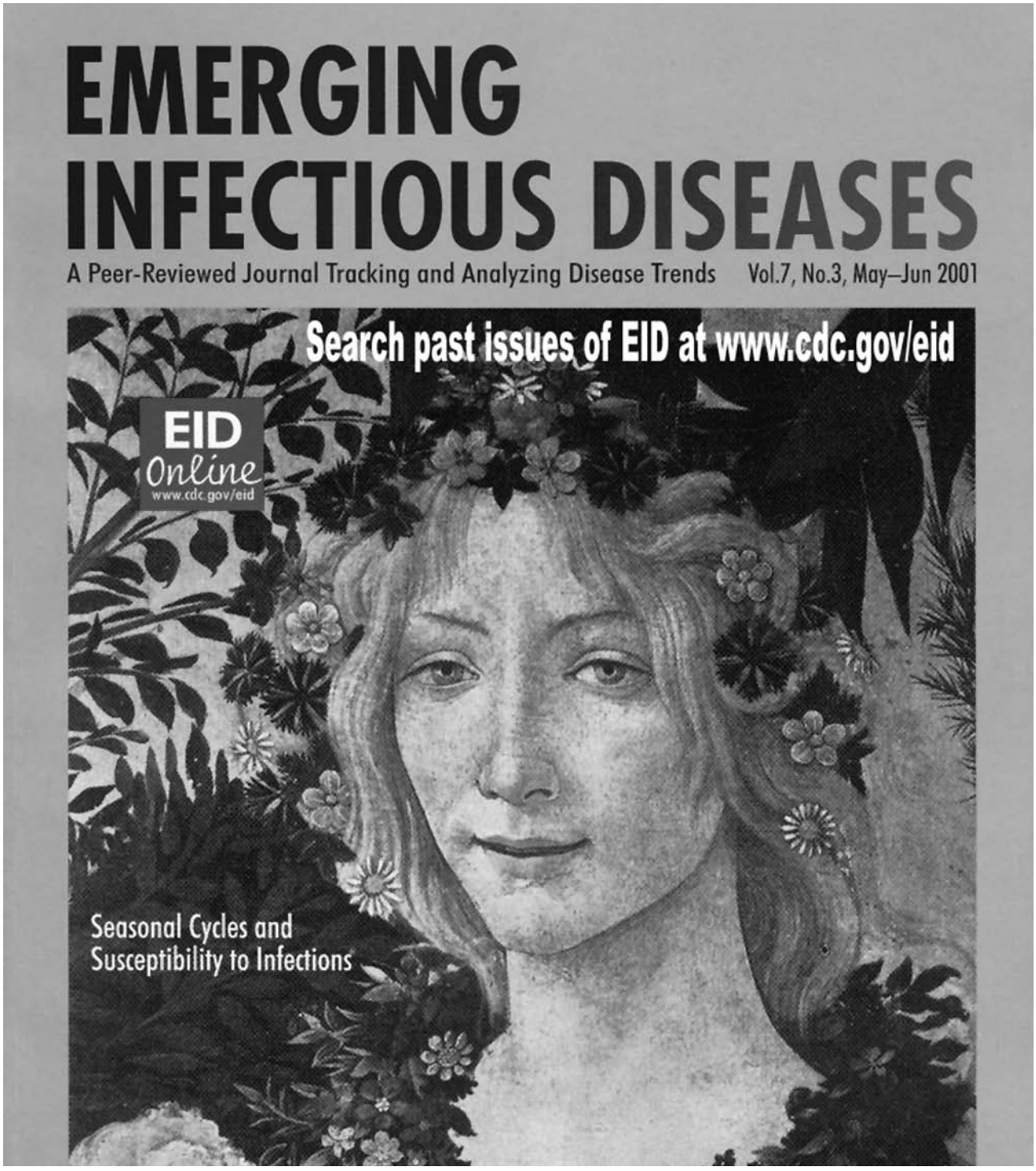

Sexual Power and HIV Risk, South Africa

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Gender power inequities are believed to play a key role in the HIV epidemic through their effects on women's power in sexual relationships. We hypothesized that lack of sexual power, measured with a four-point relationship control scale and by a woman's experience of forced sex with her most recent partner, would decrease the likelihood of consistent condom use and increase the risk for HIV infection among sexually experienced, 15- to 24-year-old women in South Africa. While limited sexual power was not directly associated with HIV, it was associated with inconsistent condom use: women with low relationship control were 2.10 times more likely to use condoms inconsistently (95% confidence interval [CI] 1.17–3.78), and women experiencing forced sex were 5.77 times more likely to inconsistently use condoms (95% CI 1.86–17.91). Inconsistent condom use was, in turn, significantly associated with HIV infection (adjusted odds ratio 1.58, 95% CI 1.10–2.27).

In 2002, the prevalence of HIV infection among South African women attending antenatal clinics was 26.5% (1). Among all 15- to 24-year-olds, 12% of women were infected, compared with 6% of men (2). While women's greater biological susceptibility to HIV helps explain this difference, a host of sociocultural and economic factors rooted in gender power inequities exacerbate women's vulnerability to infection.

Gender power inequities play a key role in the HIV epidemic through their effects on sexual relationships (3–5). In South Africa, multiple partnerships are condoned and even encouraged for men, while women are expected to be monogamous and unquestioning of their partner's behavior (5–7). Sexual refusal or negotiation may result in suspicions of infidelity and carry the risk of violent outcomes (8,9). Younger women are likely to be at a particular disadvantage, as documented by a growing body of qualitative research (6,8,10). A study of youth in a Xhosa township, for example, showed "pervasive male control over almost every aspect of [women's] early sexual experiences," enacted in part through violent and coercive sexual practices (8).

A host of economic vulnerabilities underlies young women's inability to challenge the sexual status quo. In the context of poverty, young women speak of money as the driving force for sex and relationship formation (9,11). Partnerships with men who can provide financially are essential, transactional relationships (in which sex is exchanged for material goods or other support) are common, and relationships with older men are the norm (12,13).

Several studies in the region have found that women's status or household power has effects on general contraceptive use (14–18). Very few studies have focused on younger women, attempted to measure relationship power directly, or assessed its effects on HIV-preventive behaviors. One exploratory study in Botswana found that negotiating power explained 47% of the variance in condom use (19). A study in Uganda had more mixed results, finding that relative control over sex and fertility had variable effects on condom use, depending on which partner's reports were used, and whether partner reports were in conflict (20).

A larger body of research exists on relationship power and HIV-preventive practices in the developed world, primarily among ethnic minorities in the United States. These studies have used a range of measures in their efforts to quantify relationship power, and some have had null or inconclusive results (21–23). A few studies have documented important effects, finding that women with greater sexual relationship power are more likely to use condoms or to use condoms consistently (24,25).

We undertook a preliminary exploration of the effects of sexual power on both HIV serostatus and condom use consistency by using data collected from a nationally representative sample of sexually experienced young women, 15–24 years of age, in South Africa. While investigating sexual power was not the primary aim of the survey, a set of questions on related issues was included.

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Methods

Sample

In 2003, data on sexual power, HIV risk behaviors, and HIV serostatus were collected during a nationally representative household survey of men and women 15–24 years of age. Participants were selected thorough stratified, disproportionate, systematic sampling in the country's nine provinces. A total of 11,904 interviews were completed, including 4,066 with sexually experienced young women, the subsample used in this analysis. Additional details on the survey's methods are described elsewhere (26).

Informed consent was obtained from all participants, and parental consent was obtained for those 15–17 years of age. The study was approved by the Committee for the Protection of Human Subjects, University of the Witwatersrand, Johannesburg, South Africa.

Measurement Tools

Participants completed an interviewer-administered questionnaire that covered sociodemographic factors, HIV risk behavior, and sexual power. All questions were translated from English into Sotho, Zulu, Tswana, Xhosa, Pedi, Venda, Tsonga, and Afrikaans, and then back-translated. Participants were anonymously tested for HIV by using the Orasure Oral Specimen Collection Device (Orasure Technologies Inc, Bethlehem, PA). The specimens were tested for HIV-1/2 antibodies by using the Vironostika Uni-Form II HIV-1/2 plus O MicroElisa System (Biomerieux, Durham, NC).

Measures

Our primary outcome variables of interest were HIV serostatus and condom use consistency. Women who always used condoms with their most recent partner in the past 12 months were categorized as consistent condom users; never or occasional use was categorized as inconsistent use.

Sexual power was measured through two factors: relationship control and recent experience of forced sex. Four questions were used to construct the relationship control scale, and these were drawn in part from the Sexual Relationship Power Scale (SRPS) (27), which contains 23 items in two subscales (decision-making dominance and relationship control). A pilot test of the full scale was conducted, questions were revised, and several were eliminated due to difficulties in translating concepts, lack of comprehension among pilot test participants, and space constraints in the questionnaire. Five questions remained after this process and were examined in SPSS (SPSS Inc., Chicago, IL) by using factor analysis, which verified that four of the five questions created one factor. The four questions retained, all of which required an agree or disagree response, were as follows: your partner has more control than you do in important decisions that affect your relationship; when you and your partner have an argument, your partner gets his way most of the time; your partner has more control than you do over whether or not you use condoms; your partner has more control than you do over whether or not you have sex. Reliability analysis confirmed moderate internal consistency (Cronbach's alpha 0.69). We dichotomized the four-point scale for analytic purposes, with a score of 0–2 indicating high relationship control and 3–4 indicating low control. Forced sex was measured by asking each woman if her most recent sexual partner in the past 12 months ever physically forced her to have sex (yes or no).

In addition to the sexual power variables, we examined other participant characteristics and sexual practices that have been hypothesized to effect condom use consistency and HIV status or which might confound relationships of primary interest. These variables are presented in Table 1. In particular, an index to measure condom use self-efficacy was created by using the following questions, each of which required a yes or no answer: Would you be able to use a condom every time you have sexual intercourse? Would you be able to refuse to have sex if your partner would not use a condom? Would you be able to talk about using condoms with your partner? The index had moderate internal consistency (Cronbach's alpha = 0.60).

Analysis

The final sample was weighted to represent the distribution of young people 15–24 years of age based on the 2001 census, with a particular focus on ensuring representativeness based on sex, age, race, province, and rural or urban residence. Analyses were conducted in STATA 7.0 (STATA Corp, College Station, TX) by using *svy* methods and adjusting for sample strata, primary sampling units, and population weights.

Chi-square tests for categorical variables and *t* tests for continuous variables were conducted to test for differences in HIV serostatus and condom use consistency by sexual power, HIV risk behavior, and sociodemographic factors. Variables were selected for the logistic regression models based on both a priori hypotheses and empiric findings. We hypothesized that relationship control and forced sex would primarily be associated with HIV indirectly through their effects on condom use, but that they could also be associated indirectly with HIV infection through other mechanisms, such as higher risk sexual practices (e.g., anal sex) or elements of unprotected intercourse not captured through the condom use consistency variable. Hence, we examined both the relationship between sexual power and condom use consistency and that between sexual power and HIV status.

Table 1. Weighted frequencies of HIV prevalence, sexual power, sociodemographic factors, and HIV risk behavior among sexually experienced women 15–24 years of age, South Africa, 2003

Characteristic	Weighted frequency (%)
HIV positive	21.1
Low relationship control with current partner	26.6
Did not always use a condom with last partner in past 12 mo	71.4
>1 Lifetime sexual partner	54.6
>1 partner in the past 12 mo	12.8
Most recent sexual partner in past 12 mo was a regular partner	98.2
Most recent partner in past 12 mo physically forced to have sex	3.8
Ever been physically forced to have sex in lifetime	9.6
Transactional sex with most recent partner in past 12 mo	1.3
Most recent partner in past 12 mo ≥10 y older	5.5
Age at sexual debut ≤14 y	7.8
Did not talk to most recent partner in past 12 mo about using condoms	20.5
Mean condom use self-efficacy (low 0, high 3)	2.36
Perceive self to be at high risk for HIV infection	38.4
Ever been tested for HIV	32.6
Know HIV status	18.9
Had sex >5 times in past month	10.0
Reported unusual vaginal discharge in the past 12 months	19.2
Ever pregnant	49.5
Age 20–24 y	64.1
Did not complete high school	72.9
Live in a rural area	47.3
Married	4.3
Religion not important in everyday life	13.7
Black African	88.4

Results

HIV prevalence in our sample was 21%. Most women (71%) reported inconsistent condom use, and 12.8% reported having had more than one sexual partner in the past 12 months. Almost 27% reported low relationship control, and nearly 4% reported that they had been physically forced to have sex by their most recent partner (just under 10% reported ever having been physically forced to have sex). Approximately 50% of women reported ever having been pregnant, and 19.2% reported having had an unusual vaginal discharge in the past 12 months. Almost 19% of women reported knowing their HIV status. Other information on the sociodemographic characteristics and HIV risk behaviors of the sample is presented in Table 1.

Bivariate Analyses

No significant association was found between low relationship control and HIV infection in bivariate analyses comparing women who were HIV infected to those who were not (24.1% vs. 28.3%, p = 0.31) (Table 2). Additionally, no association was found between the woman's experience of forced sex with her most recent partner and HIV serostatus (3.6% vs. 3.9%, p = 0.82). Women who were HIV seropositive were significantly more likely to have had more than one lifetime sexual partner, to be 20–24 years of age, to have not completed high school, to be of black African race, and to be single. HIV-positive women were also significantly more likely to be inconsistent condom users (78.7% vs. 69.6%, p = 0.01). No significant associations were found between HIV and recent experience of transactional sex, having an older partner, or young age at coital debut.

As we had hypothesized, inconsistent condom users were significantly more likely to report low relationship control (33.4% vs. 13.5%, p < 0.001) and to have been forced to have sex by their most recent partner (5% vs. 1%, p < 0.001) when consistent condom users were compared with inconsistent condom users in bivariate analyses (Table 3). Further, inconsistent condom users were more likely to have low condom use self-efficacy, to be in relationships with older partners, to have frequent sex with their partner, not to have discussed condoms with their partner, to be married, to have experienced early sexual debut, not to have completed high school, to perceive themselves as being at high risk for HIV infection, and to be in the older age group (20–24 years).

Multivariate Analyses

No direct association was seen between our two sexual power measures (relationship control and forced sex) and HIV infection in the logistic regression model (Table 4). Inconsistent condom users were significantly more likely to be infected with HIV (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.10–2.27). The odds of HIV infection

Table 2. Weighted frequencies and results of chi-square tests for relationship control factors, HIV risk behavior, and sociodemographic factors by HIV status among sexually experienced women 15–24 years of age, South Africa, 2003[a]

Characteristic	HIV negative (78.9%)	HIV positive (21.1%)	Chi-square p value
High relationship control (score 0–2) with current partner	71.7	75.9	0.31
Low relationship control (score 3–4) with current partner	28.3	24.1	
Last partner in past 12 mo forced to have sex	3.9	3.6	0.82
Last partner in past 12 mo did not force to have sex	96.1	96.4	
Mean condom use self-efficacy score (0 low to 3 high)[b]	2.35	2.38	0.68
Transactional sex with last partner in past 12 mo	1.3	1.5	0.89
No transactional sex with last partner in past 12 mo	98.7	98.5	
Last partner in past 12 mo ≥10 y older	5.1	7.5	0.08
Last partner in past 12 mo <10 y older	94.9	92.5	
Did not always use a condom with last partner in past 12 mo	69.6	78.7	0.01
Always used a condom with last partner in past 12 mo	30.4	21.3	
Age at sexual debut ≤14 y	7.8	7.7	0.93
Age at sexual debut >14 y	92.2	92.3	
>1 lifetime sexual partners	51.1	67.7	0.03
1 lifetime sexual partner	48.9	32.4	
Sex in past month with last partner in past 12 mo ≤5	90.3	89.1	0.49
Sex in past month with last partner in past 12 mo >5	9.7	10.9	
Talked about condom use with last partner in past 12 mo	80.2	76.4	0.24
Did not talk about condom use with last partner in past 12 mo	19.8	23.6	
Perceive self to be at high risk for HIV infection	38.3	39.0	0.89
Perceive self to be at low or no risk for HIV infection	61.7	61.0	
Age 15–19 y	40.4	19.0	< 0.001
Age 20–24 y	59.6	81.0	
Completed high school	29.3	18.7	< 0.001
Did not complete high school	70.7	81.3	
Live in a rural area	48.6	42.6	0.14
Live in an urban area	51.4	57.4	
Race Black African	85.9	97.9	< 0.001
Other race	14.1	2.1	
Religion very important in everyday life	86.5	85.9	0.8
Religion not very important in everyday life	13.5	14.1	
Married	4.9	2.3	0.002
Single	95.1	97.7	

[a]Source: National Survey of HIV and Sexual Risk Behavior among Young People Age 15–24, South Africa, 2003.
[b]*t* test for differences between means (tested with the *lincom* command in STATA for *svymeans*).

were 2.49 times greater among women with more than one lifetime sexual partner (OR 2.49, 95% CI 1.80–3.43) than among those with one partner. Women who were older (ages 20–24 years), were single, did not complete high school, lived in an urban area, and were of Black African race were also significantly more likely to be infected with HIV.

Relationship control and recent experience of forced sex were significantly associated with condom use consistency in logistic regression models (Table 5). Women who reported low relationship control were 2.10 times more likely to be inconsistent condom users (OR 2.10, 95% CI 1.17–3.78). Forced sex was found to exert particularly strong effects on inconsistent condom use: women who reported that their most recent partner forced them to have sex were 5.77 times more likely to be inconsistent condom users with that partner (OR 5.77, 95% CI 1.86–17.91). Women who reported low condom use self-efficacy were also at increased risk of inconsistent condom use: each one-point decrease in condom use self-efficacy increased the odds of inconsistent condom use by 1.86 (95% CI 1.42–2.45). The strongest predictor of inconsistent condom use was not having talked to the most recent partner about using condoms (OR 12.86, 95% CI 5.83–28.47). Married women, women who reported having frequent sex, older women (ages 20–24 years), and women who perceived themselves to be at high risk for HIV infection were also significantly more likely to report inconsistent condom use. Early coital debut, more than one lifetime sexual partner, and having an older partner were not found to be statistically significant predictors of condom use consistency.

Table 3. Weighted frequencies and p values for relationship control factors, HIV status and risk behavior, and sociodemographic factors by condom use consistency with most recent sexual partner in past 12 months among sexually experienced women 15–24 years of age, South Africa, 2003

Characteristic	Always used condom with last partner in past 12 mo (28.6%)	Did not always use condom with last partner in past 12 mo (71.4%)	Chi-square p value
High relationship control (score 0–2) with current partner	86.5	66.6	< 0.001
Low relationship control (score 3–4) with current partner	13.5	33.4	
Last partner in past 12 mo forced to have sex	1.0	5.0	< 0.001
Last partner in past 12 mo did not force to have sex	99.0	95.0	
Mean condom use self-efficacy score (0 low–3 high)[b]	2.68	2.16	< 0.001
Transactional sex with last partner in past 12 mo	1.1	1.5	0.6
No transactional sex with last partner in past 12 mo	98.9	98.5	
Last partner in past 12 mo ≥10 y older	3.2	6.5	0.01
Last partner in past 12 mo <10 y older	96.8	93.5	
Age at sexual debut ≤14 y	4.0	8.4	0.001
Age at sexual debut >14 y	96.0	91.6	
>1 lifetime sexual partners	47.7	41.7	0.23
1 lifetime sexual partner	52.3	58.3	
Sex in past month with last partner in past 12 mo ≤5	96.4	87.5	< 0.001
Sex in past month with last partner in past 12 mo >5	3.6	12.5	
Talked about condom use with last partner in past 12 mo	98.0	72.1	< 0.001
Did not talk about condom use with last partner in past 12 mo	2.0	27.9	
Perceive self to be at high risk for HIV infection	30.0	43.3	< 0.001
Perceive self to be at low or no risk for HIV infection	70.0	56.7	
Age 15–19 y	54.0	33.6	< 0.001
Age 20–24 y	46.0	66.4	
Completed high school	34.5	24.1	0.01
Did not complete high school	65.5	75.9	
Live in a rural area	38.2	51.2	0.09
Live in an urban area	61.8	48.8	
Race Black African	90.9	88.6	0.23
Other race	9.1	11.4	
Religion very important in everyday life	88.7	84.4	0.12
Religion not very important in everyday life	11.3	15.6	
Married	0.6	6.5	< 0.001
Single	99.4	93.5	

[a]Source: National Survey of HIV and Sexual Risk Behavior among Young People Age 15–24, South Africa, 2003.
[b]*t* test for differences between means (tested using the *lincom* command in STATA for *svymeans*).

Discussion

Lack of power in sexual relationships has been hypothesized to increase women's risk of HIV infection (3,4,19,28,29), but little research has shed rigorous light on this question. In this nationally representative survey, women reporting limited sexual power were not more likely to be infected with HIV. Sexual power was, however, associated with inconsistent condom use, which, in turn, was significantly associated with HIV infection.

We hypothesized that limited sexual power would increase a woman's risk of HIV infection, primarily by compromising her ability to use condoms. Women with low relationship control were significantly more likely to report inconsistent condom use (OR 2.10, 95% CI 1.17–3.78), which is consistent with the findings of other studies (25,30). This finding suggests that efforts to promote consistent condom use, a key element of HIV prevention, would benefit from efforts to enhance women's sexual power. Such efforts should not target women alone; rather, they should target and involve men as partners, essential stakeholders in improving women's sexual decision-making power.

Women reporting forced sex with their most recent sexual partner were also significantly less likely to report consistent condom use (OR 5.77, 95% CI 1.86–17.91). While only 4% of our sample reported that their most recent partner had physically forced them to have sex, approximately 10% of all women reported having experienced forced sex. Since many women may be reluctant to disclose this information in a household survey, this figure is likely to be an

Table 4. Adjusted odds ratios (AOR), 95% confidence intervals (CI), and chi-square p values for HIV infection among sexually experienced women 15–24 years of age, South Africa, 2003[a]

Characteristic	AOR (95% CI)	Chi-square p-value
Age 20–24 y (vs. 15–19 y)	2.53 (1.85–3.46)	< 0.001
Single (vs. married)	2.06 (1.14–3.71)	0.02
Did not complete high school (vs. completed high school)	2.60 (1.87–3.61)	< 0.001
Live in an urban area (vs. live in a rural area)	2.36 (1.55–3.59)	< 0.001
Black African race (vs. other race)	7.63 (3.41–17.07)	< 0.001
Did not always use a condom with last partner in past 12 mo (vs. always used a condom)	1.58 (1.10–2.27)	0.01
>1 lifetime sexual partner (vs. 1 lifetime partner)	2.49 (1.80–3.43)	< 0.001
Last partner in past 12 mo ≥10 y older (vs. <10 y older)	1.43 (0.88–2.32)	0.15
Age of first sex ≤14 y (vs. >14 y)	1.12 (0.67–1.87)	0.66
Transactional sex with last partner in past 12 mo (vs. never transactional sex with last partner)	2.03 (0.53–7.77)	0.30
Sex >5 times in past mo with last partner in past 12 mo (vs. <5 times)	1.07 (0.72–1.58)	0.73
Last partner in past 12 mo forced to have sex (vs. did not force)	0.82 (0.45–1.52)	0.55
Low relationship control (vs. high control)	1.00 (0.72–1.39)	0.99

[a]Source: National Survey of HIV and Sexual Risk Behavior among Young People Age 15–24, South Africa, 2003.

underestimate (31). In the context of masculine norms defined by male control over sexual decision-making and prevalent forced and coercive sex, many women do not have the right of refusal (6,8,10,32). In addition, our measure of physically forced sex captures only a narrow element of coercive or nonconsensual sex, which actually occurs on a continuum ranging from persuasion and trickery to force and rape (6,31).

As hypothesized, inconsistent condom users were significantly more likely to be HIV-positive (OR 1.58, 95% CI 1.10–2.26). Although this finding supports previous research on the effectiveness of consistent condom use to prevent HIV infection (33), our cross-sectional design renders it impossible to assess whether or not HIV was acquired when condom use consistency was assessed. Also possible is that the relationship operates in the opposite direction, i.e., that HIV seropositivity influences condom use consistency among persons aware of their status. Given, however, that consistent condom use is protective against HIV, the fact that fewer than one third of women reported consistent condom use indicates that most are at risk for future infection.

We did not find a direct association between our measures of sexual power and HIV infection, which suggests that the primary mechanism through which sexual power exerts effects on HIV risk is condom use consistency. Nevertheless, this preliminary analysis considered a limited subset of sexual power measures. As such, we cannot be certain that we captured the scope and dimensions of sexual power that have a bearing on HIV risk in ways other than through consistent condom use. Recent research conducted among antenatal clinic attendees who accepted routine HIV testing in Soweto adapted and validated the SRPS, including 12 items, for use in that context. Measured in this way, sexual relationship power was found to be associated with prevalent HIV infection

Table 5. Adjusted odds ratios (AOR), 95% confidence intervals (CI), and chi-square p values for not always using a condom with most recent sexual partner in the past 12 months among sexually experienced women 15–24 years of age, South Africa, 2003[a]

Characteristic	AOR (95% CI)	Chi-square p-value
Age 20–24 y (vs. 15–19 y)	1.87 (1.32–2.66)	< 0.001
Married (vs. single)	5.43 (2.06–14.34)	0.001
Did not complete high school (vs. completed high school)	1.28 (0.87–1.88)	0.2
Live in rural area (vs. live in an urban area)	1.25 (0.76–2.06)	0.37
Other race (vs. Black African race)	1.66 (1.01–2.73)	0.04
Perceive self to be at high risk for HIV (vs. low to no risk)	1.55 (1.13–2.11)	0.006
Low relationship control (vs. high control)	2.10 (1.17–3.78)	0.013
Last partner in past 12 mo forced to have sex (vs. did not force)	5.77 (1.86–17.91)	0.002
Condom use self-efficacy (0 high to 3 low)	1.86 (1.42–2.45)	< 0.001
Did not talk to last partner in past 12 mo about using condoms (vs. did talk about using condoms)	12.86 (5.83–28.47)	< 0.001
>1 lifetime sexual partner (vs. 1 lifetime partner)	1.22 (0.72–2.06)	0.45
Last partner in past 12 mo ≥10 y older (vs. <10 y older)	1.11 (0.56–2.20)	0.75
Age at first sexual experience ≤14 y (vs. >14 y)	1.62 (0.97–2.73)	0.06
Sex >5 times in past month with last partner in past 12 mo (vs. 0 times)	2.85 (1.69–4.79)	< 0.001

[a]Source: National Survey of HIV and Sexual Risk Behavior among Young People Age 15–24, South Africa, 2003.

(OR 1.53, 95% CI 1.10–2.04) (34); however, the authors did not control for condom use in their analysis, which may account for their findings. Associations between power and sexual behavior are likely to depend on sample characteristics, the conceptualization and measurement of power and risk behaviors, or a combination of these factors (35). Our nationally representative sample included young women from multiple regions, races, and cultures, among which key elements of sexual power dynamics are likely to differ.

The inherent limitations of our cross-sectional study design and the fact that we measured HIV prevalence, rather than incidence, may help explain the lack of an association between sexual power and HIV infection. The measures of sexual power described here refer to recent events in a current partnership, while infection may have been acquired in a prior partnership or under a different dynamic in the current partnership. We attempted to correct for this limitation by conducting a subanalysis among women 15-19 years of age with only one lifetime sex partner, who would likely have acquired HIV in the current partnership. Relationship control and HIV infection remained unassociated in this subanalysis (OR 0.98; 95% CI 0.76-1.26)[1]. Women who reported that their most recent partner forced them to have sex were at increased risk of HIV infection, but this association was not significant (OR 1.44; 95% CI 0.33-6.34).

Woman's sexual negotiating power is likely to be compromised in transactional sexual relationships, in relationships with older partners, and following early coital debut (28), and these factors would be expected to influence both condom use consistency and HIV risk. In this survey, the self-reported prevalence of all three of these behaviors was low: only 1.3% of women reported that they had transactional sex with their most recent partner; 5.5% reported that their most recent partner was >10 years older; and 7.8% reported having had sex at age 14 or younger. Transactional sex and early coital debut are particularly likely to be subject to underreporting due to social desirability bias. Further, young women whose first sexual encounter is nonconsensual, which is fairly common in this context (8), may not define it as "coital debut." All three of these variables were associated with increased risk of HIV infection, although the associations were not significant. Transactional sex was not associated with condom use consistency in this study. Women who reported older partners and early first sexual experience were more likely to report inconsistent condom use, though this difference was not statistically significant.

The strongest risk factor for not always using condoms with the most recent sexual partner was not having talked to that partner about condom use (OR 12.91, 95% CI 5.85–28.51). Communication between partners about contraceptive use, including condoms, has been shown to be associated with consistent use in other studies (29). In the context of our cross-sectional study, confirming the direction of the relationship is not possible: although couples who discuss condoms may be more likely to use them, those who consistently use condoms may also be more likely to discuss them. Sexual power may have an effect on partner communication and should be explored further in future research.

Given the associations between sexual power and condom use consistency, more research is warranted to assess the determinants of sexual negotiating power and to test the effectiveness of gender-sensitive HIV prevention interventions. A large national HIV prevention campaign for youth in South Africa, loveLife, has incorporated gender power issues into its media campaign by addressing issues of transactional sex, older partners, and women's lack of decision-making power in relationships (www.lovelife.org.za) (Figure). The Stepping Stones package, which is used by Planned Parenthood South Africa, also aims to challenge gender norms (32) and was recently found to increase women's sexual power in a pilot evaluation (36).

A small but growing body of research suggests that economic empowerment strategies may improve women's sexual power, with potential health benefits. In Gabarone, Botswana, economic independence was more strongly related to women's negotiating power in relationships than any other variable explored (19), and in Zimbabwe, adolescents who had their own income were significantly more likely to be consistent condom users (Megan Dunbar, pers. comm.). In the Limpopo province of South Africa, the Intervention with Micro-finance for AIDS and Gender Equity (IMAGE) program is being evaluated to determine its effect on gender-based violence, sexual behavior, and HIV incidence (37). The intervention combines a micro-finance program with a participatory learning and action curriculum. In collaboration with local partners, the University of California–San Francisco Department of Obstetrics, Gynecology, and Reproductive Sciences is currently engaged in a multisite program of research to further elucidate the linkages among economic power, sexual negotiating power, and sexually transmitted infection (STI) outcomes and to develop and test related interventions.

Debate centers around the relative effectiveness of each of the "ABCs" of HIV prevention: abstinence, being faithful to one partner, and condom use (38). However, all three elements likely play a role. Indeed, a decontextualized focus on these elements is likely to fail. HIV prevention strategies

[1]Note that relationship control was used as a continuous variable in this model as it had a more coherent relationship with HIV than did the categorical version.

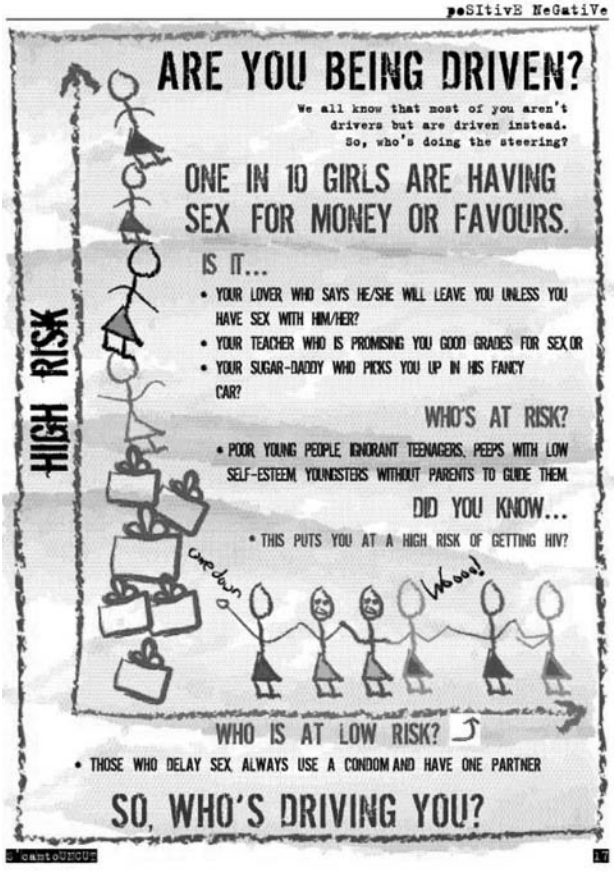

Figure. Example of message from loveLife's HIV prevention program in South Africa.

must take full account of the barriers persons, particularly women, face in bringing about behavior changes over which they may have little control. Many of these barriers are rooted fundamentally in gender inequalities.

Conclusion

For a number of years, HIV activists and researchers have highlighted the role gender inequality may play in placing women at increased risk for HIV infection. At the recent International AIDS Conference in Bangkok, United Nations Secretary-General Kofi Annan made the empowerment of women and girls a priority focus area for HIV prevention: "No less pressing, empowering women and girls to protect themselves against the virus.… What is needed is positive change that will give more power and confidence to women and girls. Change that will transform relations between women and men at all levels of society." While empiric evidence documenting the relationship between women's sexual power and their HIV risk has been in short supply, a small but growing body of research confirms that women's lack of power in relationships compromises their sexual health. While this exploratory study did not find an association between sexual power and HIV serostatus, it did confirm an association between two measures of sexual power, relationship control and forced sex, and condom use consistency. Further work is needed to refine and apply measures of sexual power and to assess the complex relationship between sexual power and HIV susceptibility in the South African context. Additional research should also aim to elucidate the underpinnings of sexual power, with a particular focus on identifying avenues for intervention.

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Women and Autoimmune Diseases

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Autoimmune diseases affect approximately 8% of the population, 78% of whom are women. The reasons for the high prevalence in women are unknown, but circumstantial evidence links autoimmune diseases with preceding infections. Animal models of autoimmune diseases have shown that infections can induce autoimmune disease. For example, coxsackievirus B3 (CB3) infection of susceptible mice results in inflammation of the heart (myocarditis) that resembles myocarditis in humans. The same disease can be induced by injecting mice with heart proteins mixed with adjuvant(s), which indicates that an active infection is not necessary for the development of autoimmune disease. We have found that CB3 triggers autoimmune disease in susceptible mice by stimulating elevated levels of proinflammatory cytokines from mast cells during the innate immune response. Sex hormones may further amplify this hyperimmune response to infection in susceptible persons, which leads to an increased prevalence of autoimmune diseases in women.

Autoimmune diseases are the third most common category of disease in the United States after cancer and heart disease; they affect approximately 5%–8% of the population or 14–22 million persons (1). Autoimmune diseases can affect virtually every site in the body, including the endocrine system, connective tissue, gastrointestinal tract, heart, skin, and kidneys. At least 15 diseases are known to be the direct result of an autoimmune response, while circumstantial evidence implicates >80 conditions with autoimmunity (2). In several instances, such as rheumatoid arthritis, multiple sclerosis, and myocarditis, the autoimmune disease can be induced experimentally by administering self-antigen in the presence of adjuvant (collagen, myelin basic protein, and cardiac myosin, respectively) (3). An important unifying theme in autoimmune diseases is a high prevalence in women (Figure 1) (4,5). Conservative estimates indicate that 6.7 million or 78.8% of the persons with autoimmune diseases are women (4).

Soon after autoimmune diseases were first recognized more than a century ago, researchers began to associate them with viral and bacterial infections. Autoimmune diseases tend to cluster in families and in individuals (a person with one autoimmune disease is more likely to get another), which indicates that common mechanisms are involved in disease susceptibility. Studies of the prevalence of autoimmune disease in monozygotic twins show that genetic as well as environmental factors (such as infection) are necessary for the disease to develop (6). Genetic factors are important in the development of autoimmune disease, since such diseases develop in certain strains of mice (e.g., systemic lupus erythematosus or lupus in MRL mice) without any apparent infectious environmental trigger. However, a body of circumstantial evidence links diabetes, multiple sclerosis, myocarditis, and many other autoimmune diseases with preceding infections (Table) (7,8). More often, many different microorganisms have been associated with a single autoimmune disease, which indicates that more than one infectious agent can induce the same disease through similar mechanisms (Table) (9). Since infections generally occur well before the onset of symptoms of autoimmune disease, clinically linking a specific causative agent to a particular autoimmune disease is difficult (Figure 2). This difficulty raises the question of whether autoimmune diseases really can be attributed to infections.

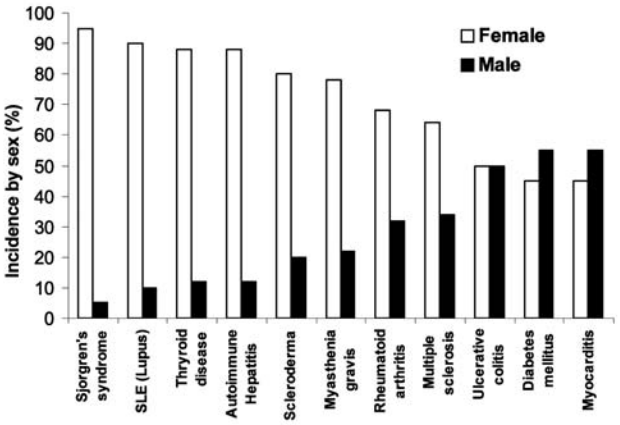

Figure 1. Major autoimmune diseases, comparing the incidence of disease in women (white bar) to the incidence in men (black bar) by percentage. Modified from (5).

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Table. Infections in humans associated with autoimmune diseases

Disease	Infection
Multiple sclerosis	Epstein-Barr virus (EBV), measles virus
Lyme arthritis	*Borrelia burgdorferi*
Type I diabetes	Coxsackie virus B4, rubella virus, cytomegalovirus (CMV), mumps virus
Rheumatoid arthritis	*Escherichia coli*, mycobacteria, EBV, hepatitis C virus (HCV)
Lupus erythematosis	EBV
Myocarditis	CB3, CMV, chlamydia
Rheumatic fever/myocarditis	Streptococci
Chagas' disease/myocarditis	*Trypanosoma cruzi*
Myasthenia gravis	Herpes simplex virus, HCV
Guillain-Barré syndrome	CMV, EBV, *Campylobacter* spp.

Are Autoimmune Diseases Caused by Infections?

To address the question of whether autoimmune diseases can be induced by infections, first autoimmunity needs to be defined. Autoimmune disease occurs when a response against a self-antigen(s) involving T cells, B cells, or autoantibodies induces injury systemically or against a particular organ. Understanding of autoimmune diseases is hindered by the fact that some level of autoimmunity, in the form of naturally occurring autoantibodies and self-reactive T and B cells, is present in all normal persons (6). Thus, on a proportional basis, developing autoimmune disease is the relatively uncommon consequence of a common autoimmune response. Although an autoimmune response occurs in most persons, clinically relevant autoimmune disease develops only in susceptible persons (Figure 2).

Given those circumstances, how can infections induce autoimmune disease? A mechanism often called on to explain the association of infection with autoimmune disease is "molecular mimicry," that is, antigens (or more properly epitopes) of the microorganism closely resemble self-antigens. The induction of an immune response to the microbial antigen thus results in cross-reaction with self-antigens and induction of autoimmunity (10). Although epitope-specific cross-reactivity between microbes and self-tissues has been shown in some animal models (11,12), molecular mimicry has not been clearly demonstrated to occur in human diseases (13). Another possibility is that microorganisms expose self-antigens to the immune system by directly damaging tissues during an active infection. This mechanism has been referred to as the "bystander effect" (14,15). However, whether pathogens mimic self-antigens, release sequestered self-antigens, or both, is difficult to determine.

In addition to antigen-specific mechanisms, nonspecific mechanisms could also lead to autoimmunity after infection (9,16). Activation of the innate immune system is essential for a protective adaptive immune response to develop; and vaccines that lack intrinsic activation of innate immunity (e.g., subunit vaccines) require microbial adjuvants to be immunogenic (17). Historically, adjuvants are considered to stimulate immune responses nonspecifically. A renewed understanding of the critical role of innate immunity in influencing the development of an adaptive immune response has led researchers to a better understanding of "the adjuvant effect" (16). Although innate immune cells do not respond to specific antigenic epitopes on pathogens, they do produce restricted responses to particular classes of pathogens through pattern-recognition receptors (PRR), such as Toll-like receptors (TLR) (18). Interaction of the microorganism component of adjuvants with PRR on innate immune cells results in activation of antigen-presenting cells and upregulation of molecules essential for antigen presentation, such as major histocompatibility complex (MHC) class II and B7–1/2, as well as production of proinflammatory cytokines. This activation of PRR by the microbial components of adjuvants stimulates the immune response in a manner similar to pathogens such as bacteria or viruses (16,18). The pathogen-specific innate immune response is not the same as the nonspecific activation that occurs after mechanical tissue damage, such as during surgery. During mechanical injury, self-antigens and cytokines are released without consistently stimulating pathogen-specific responses. Autoimmune disease rarely develops and usually resolves spontaneously, as seen in postcommissurotomy syndrome (or postcardiotomy syndrome). Adjuvants (usually bacterial, e.g., *Mycobacterium* in complete Freund's adjuvant) activate the innate immune response in the same pathogen-specific manner when administered with self-antigen; this process results in organ-specific autoimmune disease in animal models (9,16). Adjuvant alone (without self-

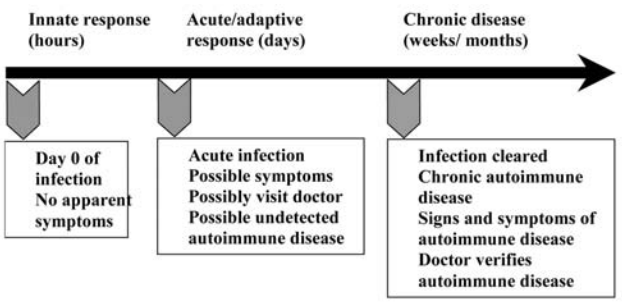

Figure 2. Infections occur before the onset of symptoms of autoimmune disease, making links to specific causative agents difficult. When a person is first infected (day 0), usually no symptoms are apparent. Signs and symptoms of autoimmune disease are clearly present and easily confirmed by physicians during the chronic stage of autoimmunity. However, the infection has been cleared by this time, making it difficult to establish that an infection caused the autoimmune disease. Modified from (16).

antigen) does not usually result in autoimmune disease, and microorganisms likely provide not only the adjuvant effect to stimulate the immune response but also the damage necessary to make self-antigens available to the immune system, resulting in autoimmune disease.

To determine whether infection can lead to autoimmune disease, direct evidence (e.g., the ability to transfer autoimmune disease), indirect evidence (e.g., the ability to reproduce autoimmune disease in animal models), and circumstantial evidence (e.g., the association of autoantibodies with disease in appropriate clinical settings) should be considered (3,6). The best evidence so far that infections can induce autoimmune diseases comes from animal models. In most animal models of autoimmunity, including myocarditis, disease has been transferred to naïve animals with autoimmune cells (splenocytes or T cells), autoantibodies (7), or both, which provides compelling evidence that infections induce autoimmune diseases by immune-mediated mechanisms.

Lessons from Coxsackievirus B3 (CB3) Myocarditis

Genetics of Susceptibility to Myocarditis

Genetic background accounts for only about one third (30%–35%) of the risk of autoimmune disease (6,19). This estimate is based on studies that compared genetically identical, monozygotic twins to nonidentical, dizygotic pairs, for which the concurrence rate can be as low as 2% to 7% (19). Therefore, noninherited factors account for the remaining (approximately 70%) risk of developing an autoimmune disorder. Yet, even identical twins do not have identical immune systems. Genes outside of the MHC contribute to the risk for autoimmune disease. However, little information is available about the function of these non-MHC genes. Recent studies have focused on regulatory signals, and considerable evidence exists that cytotoxic lymphocyte antigen–4 (CTLA-4), which provides a down-regulatory signal, influences susceptibility to autoimmunity (20). Genes that involve apoptosis, a common pathway by which immune responses generally are terminated, may also predispose persons to autoimmune disease (6).

To better understand the relationship between infection and autoimmune disease, we established a mouse model of myocarditis, or inflammation of the heart, induced by CB3 infection (9). CB3 is believed to account for most cases of myocarditis in North America and Europe; myocarditis also leads to dilated cardiomyopathy, which can result in heart failure and the need for a heart transplant (21). The same strain of CB3 that induces myocarditis in humans also induces disease in mice, which makes it an ideal pathogen to study. We found that susceptibility to myocarditis is due primarily to genes that are not part of the MHC (22). Our initial investigations into the genetic predisposition of autoimmune myocarditis involved infecting many inbred mouse strains with CB3 (22). Genetic analysis comparing susceptibility loci between susceptible and resistant strains of mice found that susceptibility to myocarditis is associated with genes on mouse chromosomes 1 and 6 that have been previously associated with other autoimmune diseases in mice and humans (M. Guler and N.R. Rose, unpub. data). In susceptible strains of mice (e.g., BALB/c, A/J), acute heart inflammation develops approximately 7–12 days after infection; the inflammation resolves by day 21, and then a chronic phase of inflammation and dilated cardiomyopathy develops from day 35 (9). In contrast, only the acute phase of the disease develops in resistant strains like C57BL/6. After mice are infected with CB3, autoantibodies are produced against cardiac myosin, the major component of heart muscle. We found that susceptible strains of mice produce higher titers of immunoglobulin (Ig) G autoantibodies that are specific for cardiac, but not skeletal, myosin, with an IgG1 response (T-helper 2 [Th2])–type) being prominent (9). The predominant cellular infiltrate during the acute phase of CB3-induced myocarditis includes macrophages, neutrophils, CD4+ T cells, and CD8+ T cells (S. Frisancho-Kiss, et al., unpub. data). Smaller numbers of natural killer cells, B cells, and eosinophils are also present. Both T-cell–mediated and autoantibody-mediated mechanisms have been shown to be important in the development of CB3-induced heart disease in BALB/c mice (9).

Knowing that cardiac myosin/adjuvant immunization induces myocarditis similar to CB3 infection, we examined the myosin sequences responsible for disease induction. We found that none of the cardiac myosin sequences were cross-reactive with viral sequences (23). Furthermore, cross-reactivity between antibodies induced by myosin immunization or CB3 infection was not observed, which suggests that molecular mimicry is not a predominant mechanism in the development of CB3-induced myocarditis (13,15,23). Viral infections can induce damage to host tissues by direct (e.g., viral replication) or indirect (e.g., nitric oxide) mechanisms. In our model of CB3 myocarditis, however, we did not observe damage to the heart cells during the acute phase of disease (9,24). We found that CB3 replicates at a relatively low level in the heart and that necrosis and fibrosis did not appear until the chronic phase of disease, after virus had been cleared from the heart (25). Thus, a low level of viral replication is sufficient to provide cardiac myosin to the immune system. Overall, our studies of CB3-induced myocarditis favor the hypothesis that autoimmune disease is induced after viral infection of susceptible mice because the pathogen facilitates the release of cardiac myosin and

nonspecifically stimulates the innate immune response in a manner similar to the effect of adjuvants (16).

Is Virus Associated with Myocarditis?

Many different microorganisms (e.g., streptococci, *Trypanosoma*, cytomegalovirus [CMV], and CB3) have been associated with the same autoimmune disease (e.g., myocarditis) (Table). We have shown that two completely different viruses (CB3, a small nonenveloped RNA virus, and murine CMV, a large enveloped DNA virus) induce a similar biphasic myocarditis in susceptible BALB/c mice (9). Although infectious CB3 or murine CMV (MCMV) can be detected during the acute phase of myocarditis, viral levels do not correlate with the severity of inflammation (9,26,27). Because viral genome can be detected after infectious virus has been cleared from the heart, latent virus may attract inflammation during the chronic stage of disease. However, when we examined the heart for the presence of latent MCMV, we found that viral genome and transcript were present in mice both susceptible to and resistant to the development of chronic disease (27). These results indicate that persistence of virus alone is not the determining factor in the development of chronic myocarditis. Yet the best evidence that active viral infection is not required for myocarditis to develop comes from the demonstration that injecting susceptible mice with cardiac myosin emulsified in adjuvant induces experimental autoimmune myocarditis (24). In fact, the pathogenesis of experimental autoimmune myocarditis closely resembles the biphasic myocarditis associated with CB3 or MCMV infection. This finding indicates that the adjuvant effect produced by infections or adjuvants during the innate immune response can lead to the development of autoimmune disease when self-antigen is present. We have found in preliminary studies that the same pattern of TLR expression is induced by CB3 and the *Mycobacterium* in complete Freund's adjuvant, which suggests a common mechanism of activation (16).

Proinflammatory Cytokines Determine the Development of Myocarditis

Key to understanding the control of susceptibility to autoimmune myocarditis was the finding that adding bacterial lipopolysaccharide (LPS), interleukin (IL)-1β, or tumor necrosis factor (TNF)-α during the innate response to CB3 infection results in the development of the chronic phase of disease in resistant strains of mice (28,29). Thus, by increasing proinflammatory cytokine production during the innate immune response to infection, genetic resistance to the development of autoimmune disease can be altered. We have found that susceptible BALB/c mice have significantly increased levels of the proinflammatory cytokines TNF-α (Figure 3A) and IL-1β (Figure 3B) in the heart during acute CB3 myocarditis. In fact, many autoimmune diseases, such as rheumatoid arthritis, are associated with increases in TNF-α and IL-1β levels, and treatments that block these cytokines have proven beneficial in animal models and clinical settings (30). We have a long-standing interest in the adjuvant effect of lipopolysaccharide (LPS) on the development of autoimmune disease (28,29,31), but only recently has LPS been shown to mediate its effects in part by increasing TNF-α, IL-1β, and IL-18 levels through TLR4 signaling (18). Recently, we demonstrated that CB3 infection increases IL-1β and IL-18 levels in the heart during acute myocarditis through IL-12Rβ1 and TLR4 signaling (26). Furthermore, the severity of acute myocarditis directly correlates with increased levels of IL-1β and IL-18 in the heart (26). Similarly, in the experimental autoimmune myocarditis model, IL-12Rβ1 signaling and increased IL-1β levels are associated with the development of myocarditis (24). This effect of LPS or TNF-α on the development of myocarditis is not limited to CB3 infection, but is also observed following MCMV infection (32). Thus, proinflammatory cytokine production is key in determining whether susceptible strains of mice develop autoimmune disease after infection.

Innate Immune Response Initiates Myocarditis

Since the innate immune response is critical in determining the development of adaptive immunity (18) and proinflammatory cytokines administered during the innate response determine whether chronic myocarditis develops, we were interested in studying early differences in the cytokine response to CB3 infection in susceptible (BALB/c) or resistant (C57BL/6) mice to see if they could provide clues to the progression to autoimmunity. We found that susceptible and resistant mice produce the same

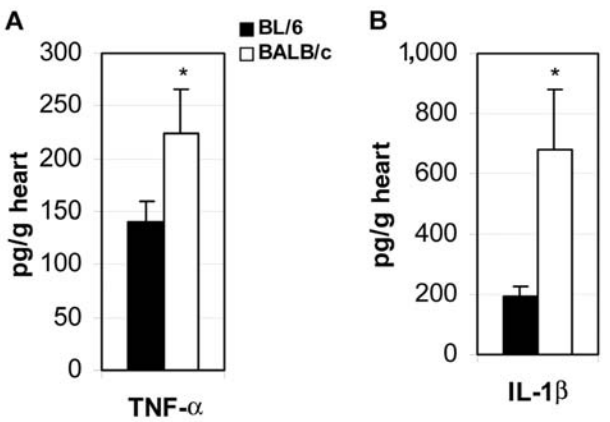

Figure 3. Proinflammatory cytokines are increased in the hearts of susceptible mice during acute myocarditis. Susceptible BALB/c mice were compared to resistant C57BL/6 mice for the level of cytokines tumor necrosis factor (TNF)-α (A) and interleukin (IL)-1β (B) in heart homogenates 12 days after CB3 infection. Data are represented as the mean ± standard error of the mean. *$p < 0.05$.

cytokine profile during the innate immune response to CB3 infection but that susceptible mice have significantly higher levels of cytokines in the heart (Figure 4) and spleen (33). The proinflammatory cytokines TNF-α (Figure 4A) and IL-1β (Figure 4B) are significantly increased in susceptible BALB/c mice at 6 and 12 hours after CB3 infection, during the innate immune response. Surprisingly, IL-4 (the prototypic Th2 type cytokine) is also significantly increased 6 hours after CB3 infection (Figure 4C). According to the current dogma, inflammatory autoimmune diseases such as myocarditis are primarily attributable to Th1 responses, with interferon (IFN)-γ as the prototypic cytokine; Th2 responses where IL-4 dominates are believed to reduce autoimmunity. Although protection against viral infections is usually associated with Th1 responses attributable to the protective effect of IFN-γ, in fact, a number of viral infections produce a mixed Th1/Th2 profile, including CB3 (24, 25,33). We also observe a mixed Th1/Th2 cytokine profile in the experimental autoimmune myocarditis model (24,34).

An elevated IL-4, TNF-α, and IL-1β response is reminiscent of the hypersensitivity reaction of mast cells during allergic responses (35). Mast cells are known to produce a rapid burst of cytokines (e.g., TNF-α, IL-1β, and IL-4) when stimulated through TLRs such as TLR2 and TLR4 (36). When we looked for mast cells in the spleen 6 hours after CB3 infection, we found that susceptible BALB/c mice had significantly more mast cells than resistant C57BL/6 mice (Figure 5) (33). We also found that TLR4 is increased on mast cells of susceptible mice immediately after infection (16). Thus, the increased innate cytokine response to CB3 in susceptible mice may be due to a mast cell–mediated response to pattern recognition sequences on CB3 (16,18,33), similar to an allergic reaction. Since the innate immune response determines whether the chronic phase of myocarditis and dilated cardiomyopathy develop in mice (29,32), early activation of mast cells may result in a delayed-type hypersensitivity reaction later, during the chronic phase of the disease (25). Mast cells are found in the human heart in increased numbers during cardiovascular disease and congestive heart failure (37). We have also observed increased numbers of degranulating mast cells during chronic CB3 myocarditis in susceptible mice with severe disease (25). So the evidence presented by the CB3-induced model of myocarditis demonstrates that virus can trigger autoimmune disease in susceptible mice by immune-mediated mechanisms. But the question

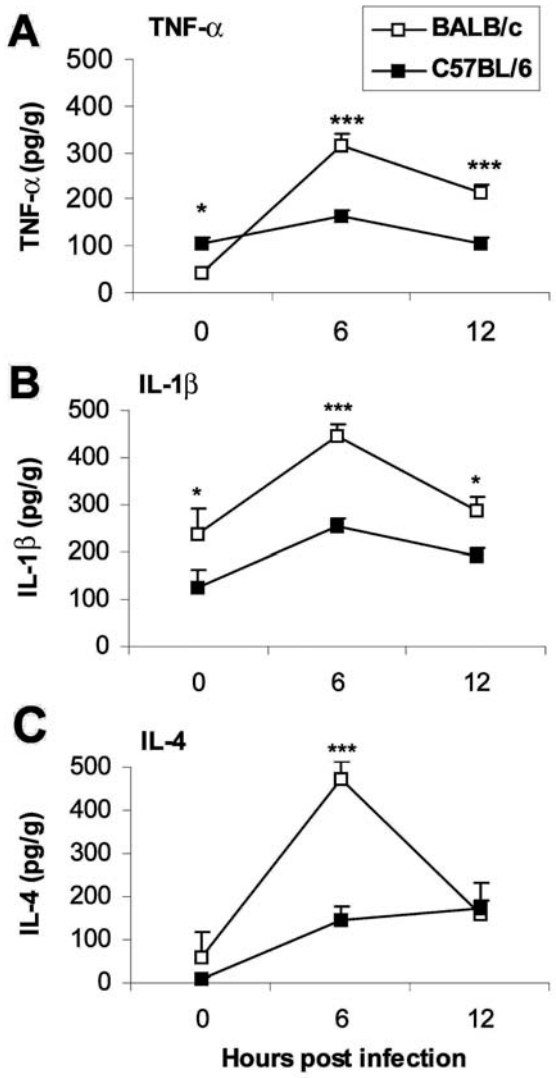

Figure 4. Proinflammatory cytokines are increased in the hearts of susceptible mice during the innate immune response. Susceptible BALB/c mice were compared to resistant C57BL/6 mice for the level tumor necrosis factor (TNF)- α (A), interleukin (IL)-1β (B), and IL-4 (C) cytokines in heart homogenates 6 and 12 hours after CB3 infection. Data are represented as the mean ± standard error of the mean. *p < 0.05; ***p < 0.001. Modified from (33).

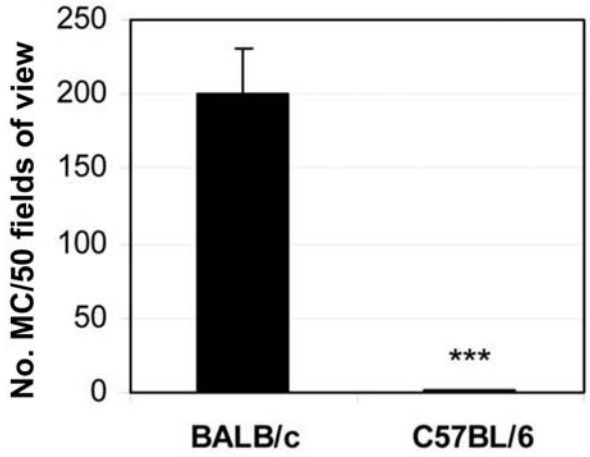

Figure 5. Mast cells are increased in the spleens of susceptible BALB/c mice 6 hours after CB3 infection. Data are represented as the mean ± standard error of the mean. ***p < 0.001. Modified from (33).

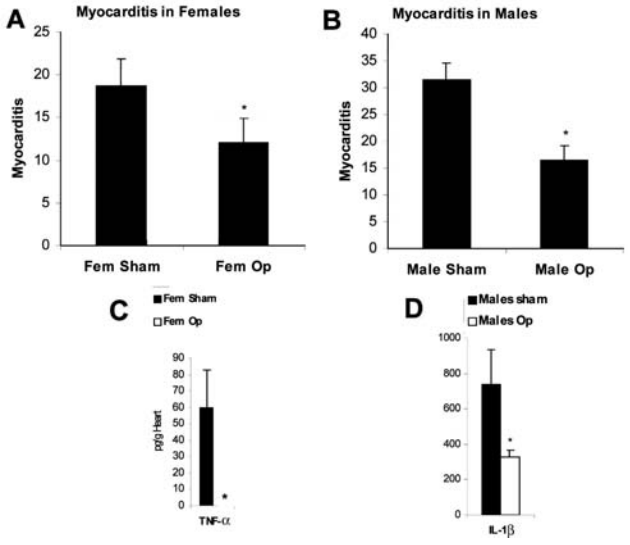

Figure 6. Sex hormones increase myocarditis in female and male mice by increasing interleukin (IL)-1β and tumor necrosis factor (TNF)-α levels in the heart. Susceptible female (A,C) and male (B,D) BALB/c mice underwent gonadectomy (Fem op/Male op) and were compared to sham-operated controls (Fem sham/Male sham) for the level of myocarditis (% inflammation) and cytokines (pg/g) in the heart after CB3 infection. CB3 myocarditis was assessed for (A) female mice and (B) male mice after the operation. Data are represented as the mean ± standard error of the mean. *, $p < 0.05$.

still remains: Why are autoimmune diseases so prevalent in women?

Why Are Autoimmune Diseases So Prevalent in Women?

Even though women's greater susceptibility to autoimmune diseases has been recognized for more than 100 years, only recently has attention focused on this topic (5). For some time, the basic immune response between men and women has been known to differ, with women producing a more vigorous immune response and increased antibody production (5,38). However, autoimmune diseases that develop in men often are more severe (39). Most of our understanding of sex differences in the immune response comes from work done in animal models. Many animal models of autoimmune disease have shown a similar sex bias, with a higher incidence of disease in women. Sex hormones, such as estrogen, testosterone, and progesterone, may mediate most of the sex-biased differences in the immune response (39). Recently, estrogens and androgens have been found to directly influence whether a Th1- or Th2-type immune response develops by interacting with hormone receptors on immune cells (38). Not only are a variety of sex hormone receptors found on immune cells, but cytokine receptors (e.g., IL-1R, IL-18R) have likewise been discovered on hormone-producing tissues, which suggests bidirectional regulation of the immune response. Furthermore, proinflammatory cytokines such as TNF-α and IL-1β stimulate the release of glucocorticoids from the hypothalamus-pituitary-adrenal axis, which regulates the inflammatory process, along with androgens and estrogens (40).

The precise interaction between hormones and the innate immune response after infection is poorly understood. However, in vitro studies of immune cells cultured in the presence of hormones have shown that estrogen significantly increases proinflammatory cytokine production (e.g., TNF-α, IL-1β) (5). In preliminary experiments studying the role of sex hormones on the development of CB3-induced myocarditis in mice, we have found that sex hormones increase inflammation and proinflammatory cytokines in the hearts of male and female mice after infection. Gonadectomy before CB3 infection reduces myocarditis in female (Figure 6A) and male mice (Figure 6B). Reduced inflammation is associated with reduced TNF-α in the female heart (Figure 6C) and reduced IL-1β in the male heart (Figure 6D). Thus, the elevated immune response in women may even further amplify the adjuvant effect of infection, thereby increasing the possibility that chronic, autoimmune disease will subsequently develop in women. With the increase in the number of autoimmune cases in recent years, the possible role of infections in exacerbating disease, particularly in women, is of rising concern.

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Contribution of Sex-linked Biology and Gender Roles to Disparities with Trachoma

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Globally, trachoma is the leading infectious cause of blindness. Survey data consistently show that trachoma-related blindness is two to four times higher in women than men. Tracing the increased risk for trachoma and its consequences for women suggests that other factors besides biology may contribute. Understanding the reasons for the excess risk for and consequences of trachoma in girls and women requires examining a number of issues: Are girls and women more biologically susceptible to the consequences of infection with *Chlamydia trachomatis*? Could other factors help explain the excess of conjunctival scarring and trichiasis in women? Do gender roles affect the risk for trachoma and its consequences? Are women more likely to have recurrence after trichiasis surgery compared to men? This article explores the answers to these questions.

Blindness is a major public health concern globally: approximately 50 million people are blind, and three times that number are visually impaired. Unless marked improvements are made in numbers of healthcare personnel, infrastructure, and use of services, 75 million cases of blindness will likely occur by 2020.

Recent evidence has shown that women account for approximately 64% of global blindness; an age-adjusted prevalence 39% higher than in men (1). Cataract, the leading cause of blindness in the world, occurs more commonly in women than men (2–3). Paradoxically, in developing countries the use of cataract surgical services among women is considerably lower than among men (4). Other leading causes of blindness include glaucoma, diabetic retinopathy, and trachoma.

Trachoma is often referred to as the leading cause of preventable blindness in the world. It is the leading infectious cause of blindness, followed by diseases such as onchocerciasis and measles. Systemic diseases such as leprosy and HIV/AIDS also lead to blindness, although much less frequently.

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Trachoma is a chronic infectious eye disease affecting marginalized population groups throughout many countries of Africa, the Middle East, Asia, and a few settings in Latin America. *Chlamydia trachomatis*, the infective agent, has no known animal reservoir. The manifestations of trachoma vary depending upon the number of episodes of infection, severity, and the persistence of infection. Trachoma generally occurs early in life through physical transmission of *C. trachomatis* to the eye by hands, flies, or cloth. The pool of chlamydiae in the community generally resides in preschool-age children (5), and transmission is easily facilitated by poor hygiene, scarcity of water, and crowded living conditions. The highest prevalence of active trachoma in hyperendemic areas is found among children 1–3 years of age. Adult women are also more likely to have evidence of active disease and infection.

A single episode of infection will not lead to sequelae; however, repeated bouts of infection and active disease as well as persistent infection will lead to scarring of the upper tarsal conjunctiva. Approximately 10% of children have persistent infection and many are actively and consistently shedding infectious agent (6). The severity of active disease will generally dictate the severity of scarring. Among those with tarsal scarring, a small proportion will have thickening of the tarsus and deformation of the lid, whereby the malposition of eyelashes leads to abrasion of the cornea and, in some cases, corneal ulceration and scarring. Consequently, trachoma occurs throughout patients' lives, exhibiting different signs and symptoms at different stages; Figure 1 gives an example of the changes in disease and its sequelae in trachoma-endemic countries.

Estimates of the number of people affected and blinded by trachoma have been recently revised; approximately 80–85 million people now have active trachoma, approximately 8 million have trichiasis, and 3 million are blind. Most of those affected are found in sub-Saharan Africa, the Middle East crescent, and parts of Asia. The distribution of trachoma corresponds with that of poverty in much of Africa and Asia. Conditions that facilitate the transmission

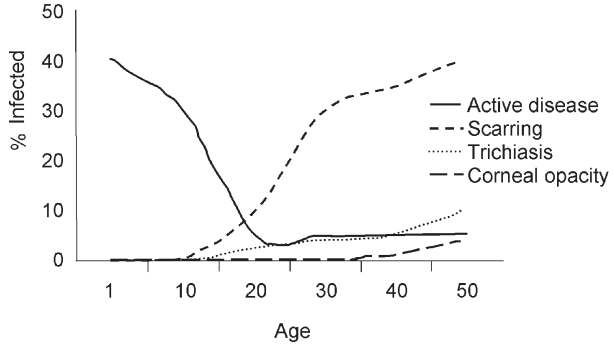

Figure 1. Trachoma as a disease that occurs throughout the life of a person.

of *C. trachomatis*, such as household crowding and poor access to and use of water, define risk (7). Because of changes in disease endemicity, active disease and trachomatous trichiasis are less correlated than they were 50 years ago; for example, active trachoma has disappeared in most areas of China, where it was once endemic. There are, however, approximately 2.5 million people in China blind because of trachoma (8). Trichiasis also remains common in countries such as Vietnam, where active disease rates are relatively low. Trachoma has been eliminated as a public health problem in these settings and others (such as Tunisia, Saudi Arabia, and Oman) through improved socioeconomic status, improved environmental and public health infrastructures (water supply, latrines), and changed behavior. Nevertheless, because infections accumulated in the past, trichiasis is likely to develop in many persons in these countries.

Productivity losses attributable to trachoma are conservatively estimated at U.S.$2.9 billion annually. This figure is likely an underestimate of the social cost of the disease (8).

Trachoma as a Gender-associated Health Issue

Survey data from virtually every trachoma-endemic setting have consistently shown that trachoma-related blindness is two to four times higher in women compared to men (9–12). Survey data also show that women have an excess risk for corneal opacity, trichiasis, and scarring; women account for 60% to 85% of all cases of trichiasis in the community (11–14). Tracing the excess risk for and complications of trachoma borne by women through the course of disease suggests that factors other than biology are involved. While evidence shows that, by the age of 40, women are more likely to have severe conjunctival scarring compared to men, the relative effect is not as high as expected, if a linear association is assumed. The further back along the course of the disease in a patient, evidence becomes less and less clear. In young children, the focus of most active trachoma in a community, the prevalence of active disease seems to vary, with just a slight excess risk for girls. In some surveys, such as recently in Dalocha District in Ethiopia, while 11 of 18 trichiasis cases were in women, in children <10 years of age, 21.1% of boys and 13.5% of girls had active trachoma (13). However, in another district in Ethiopia, girls and women were 1.63 times more likely to have active trachoma compared to boys and men (11). Preschool girls in Tanzania had slightly higher rates of active trachoma than boys; including adults in the findings showed that female patients had a twofold excess risk for active trachoma compared to male patients (14). In most settings, the differences in prevalence of active trachoma between girls and boys are not as striking as they are in women and men (12,15).

Excessive Effect of Trachoma on Women

Understanding the reasons for the excess risk for and complications of trachoma in girls and women requires examining a number of issues. Are females more biologically susceptible to the consequences of infection with *C. trachomatis*? Could other factors (e.g., number of episodes, persistence of disease, higher bacterial loads) help explain the excess conjunctival scarring and trichiasis in women? Do gender roles affect the risk for trachoma and its consequences? Are women more likely to have recurrence after trichiasis surgery compared to men?

Biologic Susceptibility to Consequences of Infection with *C. trachomatis*

Research in developing countries has not shown that women or girls are more biologically susceptible to the consequences of infection with *C. trachomatis*. However, research in industrialized countries has demonstrated a higher prevalence of dry eye syndrome in women, likely due to hormonal factors. If these findings are applied to trachoma-endemic settings, they would suggest that corneal damage is more likely to develop in women with trichiasis than men. The paucity of longitudinal data analyzed by sex limits our ability to confirm this hypothesis.

Other Factors Explaining Excess Conjunctival Scarring and Trichiasis in Women

Recent research in Tanzania suggests that, while girls have only slightly higher prevalence of active disease than boys, they account for most of the community load of the community load of *C. trachomatis* infection (A. Solomon, pers. comm.). In a different population in Tanzania, when the group of children with a heavy bacterial load were compared to noninfected persons, those with a heavy bacterial load were more likely to be younger and to be female (odds ratio 1.64, 95% confidence intervals 1.1–2.5) and to live in a house with at least one other person with heavy

infection (16). In a separate study in the same district, antimicrobial treatment was provided to all residents. At the 2-month follow-up, the predictors of infection were being younger and female and having trachomatous inflammation at baseline assessment before treatment. At 6 months, the strongest predictor of infection was infection at 2 months; 95% of those with a severe infection at 2 months were infected at 6 months (17). Despite high rates of antimicrobial coverage in this community, *C. trachomatis* was reemerging, even among those treated.

These studies suggest that infection loads are higher in girls and women and that persistent infection is more common in girls. Longitudinally, this hypothesis is supported by the 7-year follow-up results on conjunctival scarring. Of girls with severe active trachoma at the beginning, 33% eventually had scarring compared to 22% of boys with similarly severe active trachoma (18).

Few studies have measured infection with *C. trachomatis* in adults. In a study of women, infection in adulthood, although not common, increased the risk for trichiasis 2.5-fold (19). The few studies with information on infection show that adult women are more likely than adult men to be infected (5,20). These data justify treating adults, particularly women.

In a follow-up study of women in Tanzania, evidence for persistent infection existed, as several women were infected at follow-up with the same genovar (21). Whether men have more or less susceptibility to persistent infection is not known.

Effect of Gender Role on Risk Factors for Infection

Women and girls are the primary caregivers in most societies in developing countries. Proximity to children exposes women to repeated infection more than men and is likely a primary reason for the greater effect of active disease (22). The close association of mothers with children makes them more likely to continue to acquire infection and exposes them to the risk for persistent infection. Ongoing infection and scarring may explain the almost four times greater risk compared to men of developing trichiasis. In central Tanzania, women with preschool-age children appeared more likely to have active trachoma than similarly aged women without preschool-age children. Young girls have the role of childcare in this setting, and active disease is associated with the status of mother or caretaker (14). However, a case-control study of trichiasis in women did not find a significant difference between childcare activities in those with trichiasis compared to those without trichiasis; the study design did not permit an evaluation of infection in the children themselves, which is the key factor (23). That study did find an increased risk in women whose mothers also reported trichiasis, which suggests a possible genetic or shared environmental component to trichiasis. The absence of rigorous behavioral research has limited our ability to understand how gender roles contribute to the progression from infection to clinical disease and its sequelae.

In many Islamic countries the use of kohl and other traditional products for preventing eye diseases, treating eye diseases, and "brightening" the eyes is common and can be implicated in disease transmission within the household and community (24). In addition, some of these traditional products are applied by everting the lid, moistening the product with saliva, and rubbing the compound directly onto the tarsus. This procedure may further scar the tarsus and spread bacteria from the nasopharynx. These products are used among both young boys and girls, but continued use in adulthood is limited primarily to women. This practice may be another way in which gender roles contribute to the excessive effects of trachoma in women.

Recurrence after Trichiasis Surgery

Recurrence after surgery to correct trichiasis is not uncommon. Recurrence rates reflect both poor quality of surgery (recurrence usually occurring within 6 months of surgery) or other pathologic processes (e.g., continued contracture of the tarsal conjunctiva, reinfection). Recurrence, measured cross-sectionally, may reflect both of these conditions; measured prospectively, determining the apparent contribution of each factor is easier. Most studies of the outcome of trichiasis surgery had few patients enrolled and lacked adequate power to compare differences between men and women (25). Omani women and men, with 3- to 5-year follow-up data, had unequal rates of recurrence. Overall, 61.3% of surgeries in women were associated with recurrences compared to 48.9% among men (26). West et al., in their large series of cases in Tanzania, found no difference by sex in recurrence rates up to 8 years (E. West, pers. comm.). Cross-sectional studies indicate that women are more likely to have recurrence compared to men. In the recent Egyptian study, trichiasis recurred after surgery in 44.4% of women compared to 37.7% of men (10).

Possible reasons for the differences are multiple and may overlap: Women may have had more severe trichiasis before surgery, which is a known risk factor for recurrence (27). In some settings, women use surgical services less or may wait until trichiasis is more advanced before surgery. Finally, reinfection may play a role in recurrence. As noted, infection in adulthood increases the risk for trichiasis 2.5-fold (19). In the Omani study (26), recurrence was approximately three times higher in persons with infective conjunctivitis compared to those without conjunctivitis. All these potential explanations point to gender role–mediated factors more than sex-linked factors. Gender roles in most societies in trachoma-endemic countries account for

the variation in prevalence of infection and sequelae of infection seen in men and women (Figure 2).

Public Health Approaches to Trachoma Control and Gender Equity

Eliminating trachoma as a blinding disease is the goal of the Alliance for the Global Elimination of Trachoma by 2020. The Alliance has adopted a four-part strategy, referred to as the SAFE strategy, which includes surgery to correct trichiasis, antimicrobial agents to treat active trachoma, and face washing and environmental changes to prevent transmission. Adopting the SAFE strategy, while not explicitly gender-sensitive, would necessitate considering gender in implementation.

Few national trachoma control programs monitor use of trichiasis surgery separately for men and women. Fewer still have adequate information on the proportion of trichiasis patients who have had surgery. This lack of this information limits evaluation of program progress, gender based or not. Data from the Tanzania and Vietnam programs suggest that these countries have gender equity in trichiasis surgery (28). However, programs directed at increasing the number of persons receiving surgery to correct trichiasis have generally not been explicitly gender-sensitive, and publications on uptake of services have rarely compared men and women. Gender equity in use thus remains unknown in most settings.

Similarly, trachoma control programs have tended to measure antimicrobial coverage as a single, community-wide or districtwide measure, without assessing rates of compliance by age and sex. Research on compliance from Rombo district in Tanzania showed that compliance with azithromycin treatment was higher among women (80.2%) than men (73.3%). However, as pregnant women are not eligible to receive azithromycin and must use topical tetracycline, interpreting coverage findings is not straightforward (29). The authors suggested that, since childcare is primarily the concern of women, they were more likely to attend the distribution of azithromycin by bringing their children and thus are more likely than men to receive drugs for themselves. Furthermore, the authors suggested that patient or recipient expectations contributed to compliance and that the expectations of women were influenced to a greater extent than those of men by their children's illness (N. Desmond, pers. comm.). Current recommendations promote a minimum antimicrobial coverage (whole population) of 80%; evaluation is needed to assess if women are more or less likely to get an antimicrobial agent.

Although the antimicrobial agent is currently donated free-of-charge, the cost of distribution remains high (approximately U.S$0.50 per dose) (30). This cost is borne by various governmental and nongovernmental agencies; however, how long this can continue is not clear.

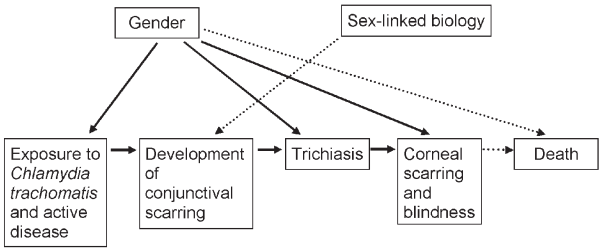

Figure 2. Contribution of gender and sex-linked biology to the progression to blindness in trachoma.

Willingness to pay for research in Tanzania has demonstrated that those at higher risk for trachoma were less willing to pay for future treatment. This group included female-headed households (31). Only higher maternal education was associated with willingness to pay.

Approaches to preventing trachoma in the SAFE strategy, namely, face washing and environmental changes, have not been researched to the same extent that surgery and antimicrobial use have. Research in the early 1990s demonstrated the effectiveness of face washing in trachoma reduction (32). Cross-sectional studies of risk factors have consistently showed a strong association between the presence of active trachoma and the absence of good sanitary conditions (primarily the absence of latrines and the high concentration of flies). Assessment of environmental conditions (including water supply) is household- or community-based, rather than individually based, thus limiting the ability to evaluate gender-specific characteristics. Nevertheless, the fact that women and girls are primarily responsible for water collection, face washing, and cleaning (if done) of latrines suggests that introducing improved infrastructures will have the greatest effect on women, both in terms of eliminating trachoma and improving quality of life. Women's and girls' roles also suggest that most hygiene and environmental components of trachoma control will fall to women as well. Thus, for example, in the absence of water in the villages, convincing women to use scarce water that they must collect for washing purposes is difficult.

Trachoma remains a major problem, particularly among girls and women, in much of sub-Saharan Africa, areas of the Middle East crescent, and pockets of Asia and South America. Eliminating trachoma, while possible, will require a rededication to prevention strategies and a focus on disease control as a gender-sensitive intervention.

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Rubella Elimination and Improving Health Care for Women

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In the Americas, the Pan American Health Organization supports strategies for the appropriate control and elimination of vaccine-preventable diseases, especially if the strategies are designed to reduce health inequities, strengthen the political commitment for immunization services, and promote the culture of prevention. In September 2003, the 44th Directing Council of the Pan American Health Organization adopted a goal to eliminate rubella and congenital rubella syndrome by 2010. One of the main objectives of this initiative is improving women's health, consistent with achieving the Millennium Development Goals. An important component of rubella elimination is conducting vaccination campaigns for men and women of childbearing age to reduce rapidly the number of people susceptible to rubella infection. From 1998 to 2002, the English-speaking Caribbean, Chile, Costa Rica, Brazil, and Honduras conducted mass rubella vaccination campaigns aimed at adults. Vaccination coverage reached >95% in each country with an exception of the Caribbean, where the coverage was 80%.

The Pan American Health Organization (PAHO) supports strategies that encourage political commitment, reduce inequities in health, and enhance the culture of prevention (1). In that context, the initiative to eliminate rubella and congenital rubella syndrome was adopted by the directing council of PAHO in September 2003 (2). Political commitment to expand coverage and reach children and women who generally do not receive health services is important to the success of this initiative. The work of the national immunization program in the Americas is not limited to children and includes reaching the adult population, especially women of childbearing age.

The initial purpose of the Expanded Program on Immunization (EPI) in the Americas, launched in 1977, was to reduce illness and deaths from prevalent childhood diseases that could be prevented with vaccination (3). EPI accomplished this purpose by setting up and expanding permanent services within the framework of primary health care and by creating the necessary mechanisms for effective, large-scale application of existing knowledge and technology.

Planning and developing EPI led to eradicating polio and progress toward eliminating measles. The goal of eliminating neonatal tetanus as a public health problem was also met and sustained. Now, the region is challenged with eliminating rubella and congenital rubella syndrome by 2010. One of the main objectives is improving women's health, which is also one of the major Millennium Development Goals in health (4).

Eliminating polio from the Americas, with a reduction in the number of reported cases from 6,653 in 1970 to 0 in August 1991, is often sited as an example of effective collaboration among governments, nongovernmental organizations, the private sector, and local communities (5). Collaborators participated in implementing all aspects of operations, including financing, training, surveillance, vaccinating, and mobilizing mass media. The partners also helped mobilize volunteers to access hard-to-reach populations for vaccination.

The experience and concrete products obtained during the years of the polio elimination initiative benefited the ministers of health by giving them the necessary confidence and credibility for allocating adequate resources to the current vaccination programs and embarking on new initiatives. The countries now cover >80% of the expenditures of routine vaccination programs, including the purchase of vaccines.

Building on the successful experience of Cuba and English-speaking Caribbean countries in interrupting endemic transmission of the measles virus, the ministers of health adopted a resolution at the 24th Pan American Sanitary Conference in 1994 to interrupt indigenous measles transmission in the Americas by the year 2000. From 1990 to 2002, the number of reported measles cases declined by 99.2% in the Americas, with measles cases plummeting from ≈250,000 cases in 1990 to 2,109 cases in 2002 (6). Since September 2001, no viruses of the D6 strain have been identified in the Americas, and the last confirmed infection with d9 genotype was reported in

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November 2002. In 2003, 105 cases were reported. Of these, 44 were in Mexico and 45 in the United States (26 were indigenous and 19 imported).

As a consequence of administering at least two doses of tetanus toxoid to women of childbearing age in high-risk areas and ensuring that all cases were fully investigated, the number of reported cases of neonatal tetanus declined. In 2003, only 116 cases of neonatal tetanus were reported; ≈50% of them were in Haiti, the only remaining country in the Americas where neonatal tetanus continues to be endemic (7).

Eliminating Rubella and Congenital Rubella Syndrome from the Americas by 2010

Cuba was the first country to eliminate rubella and congenital rubella syndrome. The last reported case of congenital rubella syndrome in Cuba occurred in 1989 and the last reported case of rubella in 1995. With measles elimination as a guide, similar strategies were proposed and implemented for rubella and congenital rubella syndrome elimination. This milestone was largely achieved by implementing two mass vaccination campaigns from 1985 to 1986. Initially, the Cubans tried to reach women 18–30 years of age and, then, children 1–14 years of age (8). In the rest of the region, the strengthening of measles surveillance demonstrated that circulation of rubella virus was widespread and that congenital rubella syndrome was an important public health problem (Figure). In response to the circulation of the rubella virus and the potential for the emergence of rubella epidemics, the countries of the Caribbean launched a subregional initiative in 1997 to eliminate rubella and congenital rubella syndrome.

The adopted strategies included rapidly reducing the susceptible population and implementing high-quality surveillance. The specific strategies included using a rubella vaccine in routine childhood vaccination programs, aiming vaccination campaigns at men and women of childbearing age, developing integrated measles and rubella surveillance systems, implementing a congenital rubella syndrome surveillance system, and supporting improved laboratory capacity for isolating rubella virus (9,10).

Beginning in 1999, other countries accelerated their strategies for rubella control and the prevention of congenital rubella syndrome. Chile (1999), Costa Rica (2001), Brazil (2001–2002), Honduras (2002), and El Salvador and Ecuador (2004) have conducted mass rubella vaccinations among adults. They combined this strategy with the introduction of the rubella vaccine into their national childhood vaccination programs. This combination strategy is designed to rapidly reduce rubella virus circulation, while preventing a shift in the prevalence of the disease to susceptible young adults, especially women of childbearing age. The Caribbean, Costa Rica, Honduras, El Salvador, and Ecuador vaccinated men as well as women, while Chile and Brazil vaccinated only women of childbearing age. The countries that only vaccinated women have reported cases of rubella in 2004; the last congenital rubella syndrome case in Chile was in 2001 and in Brazil in 2004 (11).

By September 2004, a total of 43 countries and territories in the region had introduced vaccines containing the rubella antigen (MR or MMR) in their national child vaccination program. The only remaining country, Haiti, should do so in 2005.

The experiences of Cuba and the English-speaking Caribbean countries strengthened the commitment for rubella elimination in Chile, Costa Rica, Brazil, and Honduras before the regional elimination initiative was adopted by the directing council of PAHO. These experiences showed that implementing strategies and recommendations to eliminate rubella and congenital rubella syndrome was feasible. In addition, rubella elimination provided opportunities for strengthening the health system by building partnerships and involving national and local authorities (Table)

In the English-speaking Caribbean, the cost-benefit ratio for vaccination was 13.3:1, and the cost-effectiveness was U.S. $2,900 per prevented case of congenital rubella syndrome. The comprehensive vaccination plan for adults included strategies for safe injections and monitoring adverse events during campaigns. In Chile, health promotion was well-planned, and awareness among women about their own health and their family's increased.

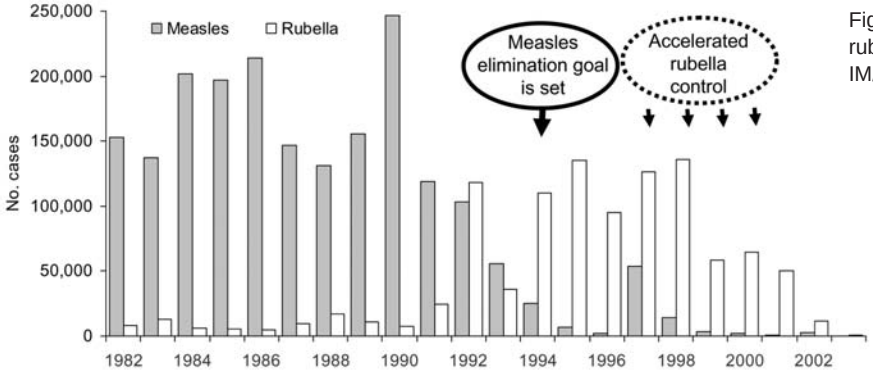

Figure. Number of confirmed measles and rubella cases, Americas, 1982–2003. Source: IM/Pan American Health Organization.

Table. Rubella and congenital rubella elimination[a,b]

Time	Country	Target group	Vaccine used	Coverage achieved (%)
1998–2001	English-speaking Caribbean 18 countries	2.16 million men/women 20–29 y	MR and MMR	Average 80[c] Range 64–97
1999	Chile	2.5 million women 10–29 y	R	98
2001	Costa Rica	1.6 million men/women 15–39 y	MR	98[c]
2001	Brazil	27 million, women 12–39 y[d]	MR	95
2002	13 states 11 states			
2002	Honduras	3.3 million men 5–39 y women 5–49 y	MR	98 Men 95 Women 98
2004	El Salvador	2.8 million men/women 15–39 y	MR	99 Men 93 Women 99
2004	Ecuador	4.8 million men/women 16–39 y	MR	100 Men 100 Women 100

[a]CRS, congenital rubella syndrome; R, rubella containing vaccine; MR, double viral vaccine, measles/rubella containing vaccine; MMR, triple viral vaccine.
[b]Source: 12–18.
[c]Men/women vaccinated in equal proportions.
[d]Some states modified the age of the group based on the year of the vaccine introduction.

In Costa Rica, the decision to conduct the campaign was based on epidemiologic information and cost benefit analyses. The president of the republic declared the event official by executive decree, which greatly facilitated intersectoral coordination of public and private institutions. The strategies to reach older populations in urban and rural areas differed. In urban areas, vaccination teams began with captive populations and ended with door-to-door "mop-ups." In rural areas, the campaign began in more isolated places and moved towards city centers with door-to-door "mop-ups" or micro-concentration. Enlisting the participation of medical societies and professional associations and the active involvement of health workers were essential. Blood banks had to be involved so that the nation's blood supply was not threatened. The monitoring of post-vaccination adverse events and immediate investigation of events was considered a top priority. Extensive follow-up studies of women who were vaccinated and not known to be pregnant demonstrated that an increased risk for adverse events did not exist.

In Brazil, social mobilization was the key to the success of a vaccination campaign aimed at adults. Health professionals recognized as leaders and decision makers in the country were called upon to explain the campaign and clarify issues. A rapid response plan was put together in each state to deal with crises or adverse events of vaccination, and a telephone hotline was set up for the public. The most common questions were where to go to be vaccinated (36%), what to do if a pregnant woman had been vaccinated by mistake (14%), and other questions about adverse events (10%). Health authorities used the rapid evaluation tools to determine which groups of women had not been vaccinated and designed effective methods to reach them. In Honduras, adult men in marginal areas rarely seek health services, so the campaign served to increase health contacts.

In El Salvador, vaccination methods implemented during the first 2 weeks were aimed at captive populations in work and study centers and in high-transit areas or areas with high populations. House-to-house vaccination was continued after normal work hours to ensure that the adult population was at home. In addition to promotion during the campaign, the plan for social communication and mobilization launched activities aimed at motivating blood donors and avoiding blood shortages before the campaign.

In Ecuador, a presidential decree urging public and private sectors to participate was helpful. A total of 6,722 rapid coverage monitoring surveys were performed in 2,006 health units, and 75% of municipalities reported coverage >95%. When coverage was not recorded, the surveys helped to identify susceptible groups and implement "mop-up" activities. The social communication showed that the source of information from health units, TV, and radio was most effective. School source information was also helpful.

Surveillance

To accelerate the strategies to eliminate rubella and congenital rubella syndrome, countries were challenged to improve surveillance of congenital rubella syndrome, while strengthening the already established integrated measles and rubella surveillance system. Improving congenital rubella syndrome surveillance required that health authorities more effectively identify and monitor women of childbearing age who may have contracted rubella during their pregnancy.

The reporting network of Latin America and the Caribbean includes nearly 22,000 reporting sites. The network encourages collaboration between the public and private sectors. The network has contributed to the formation of trained epidemiologists with experience in surveillance, disease control, and operations research to respond to new, emerging, and reemerging infectious diseases, such as cholera, influenza, and yellow fever (19). The surveillance work has also contributed to women having more frequent contact with prenatal services.

Implementing congenital rubella syndrome surveillance is particularly important during the initial phase of elimination to monitor effectiveness of congenital rubella syndrome prevention. Moreover, all countries are setting up consultation teams in hospitals for congenital infections with the active participation of neonatologists. Well-baby check-ups are used to look for congenital malformations. As a by-product, national registries for identifying all congenital malformations and ensuring their follow-up are being strengthened.

Discussion

Strengthening health services by implementing high-quality congenital rubella syndrome surveillance, periodic well-baby check-ups, or setting up areas for consultations for congenital infections is essential for high-quality, comprehensive perinatal care. The use of these perinatal information systems improves the monitoring of children with congenital malformations and provides them with increased contact with rehabilitation and special education services. The by-product of such efforts is providing patients with better, more specialized care and referrals.

Empowering women with the knowledge of prevention is a key strategy for improving the quality of health care for women (20). The communication and social mobilization strategies of the rubella and congenital rubella syndrome elimination initiative are designed to enable women to make their own choices, exercise their rights, and demand improved health care.

Regional perinatal information systems, such as the Latin-American Center for Perinatology and Human Development and the Congenital Malformation Latin-American Collaborative Study, help to improve surveillance and services for newborns (21). These systems also provide valuable information on maternal deaths and are important in investigating all maternal deaths.

The rubella elimination initiative offers an opportunity to put adults in more frequent contact with the health services. In some communities, adult men also make key decisions affecting care-seeking for women and their newborns. Thus, men must be aware of women's needs, risks, and warning signs. Promoting men's roles as partners and fathers is essential for enlisting their participation and support, a message that is always conveyed during adult vaccination campaigns (22). In some communities, mothers may more easily gain access to specific health services if they have the full support of other family members, especially their husband.

A major challenge in women's and perinatal health care is ensuring universal access, which means bring healthcare services high-risk communities where poor and underserved groups live. Because the vaccination campaign is aimed at 100% of the population, inequities based on sex, ethnicity, social class, race, and geographic distribution are reduced. This experience also greatly contributes to the reduction of inequities of maternal health outcomes (23).

To improve the health of all persons, scientists, health providers, administrators, business, media, and religious leaders, and all other sectors of society must be enlisted. The most fundamental challenges faced by the rubella elimination initiative are the mobilization and coordination of all sectors in a joint cause. Promoting women's health care and safe motherhood should be well grounded in a multisector approach that requires carefully building and maintaining partnerships.

Immunization services aimed at protecting children have played a decisive role in improving childhood health in the Americas. The foundation for expanding vaccination to other age groups should generate opportunities for strengthening health services for adults. Countries in the Americas are working hard to extend the benefits in the fields of social mobilization, community participation, staff education, epidemiologic surveillance, and program management. Countries are also committed to ensuring that the rubella elimination initiative plays a major role in improving women's health care.

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Globalization and Infectious Diseases in Women

Carol Bellamy*

Women have an enhanced vulnerability to disease, especially if they are poor. Indeed, the health hazards of being female are widely underestimated. Economic and cultural factors can limit women's access to clinics and health workers. The World Health Organization (WHO) reports that less is spent on health care for women and girls worldwide than for men and boys. As a result, women who become mothers and caretakers of children and husbands often do so at the expense of their own health. The numbers tell the story: the latest (2003) World Health Report showed that, globally, the leading causes of death among women are HIV/AIDS, malaria, complications of pregnancy and childbirth, and tuberculosis.

One might have thought that by the year 2004, gender myopia would be far less of a factor. For we now know that only by opening up educational, economic, social, and political opportunities for women can the world ensure progress in stabilizing population growth, protecting the environment, and improving human health, starting with the well-being of young children.

All these links and more were set forth in compelling terms in 1990, at the watershed World Summit for Children, where world leaders vowed to give every child a better future, and in subsequent global gatherings on environment, population, and the pervasive challenges to human rights, including the rights of women and girls. More recently, those commitments were reaffirmed by governments in connection with their embrace of the United Nations (U.N.) Millennium Development Goals, the action plan of the 2002 General Assembly Special Session on Children, and United Nations Children's Fund (UNICEF) Medium Term Strategic Plan.

Moreover, the positive aspects of globalization have begun to make a difference in areas where women suffer disproportionately, especially from two leading diseases with high death rates, malaria, and HIV/AIDS. Malaria, for example, can be prevented and treated by available cost-effective interventions, including insecticide-treated nets that can cut malaria deaths by 20% and reduce infections by 50%. During pregnancy, malaria complications and deaths can be prevented by administering two doses of an antimalarial drug (sulfadoxine-pyrimethamine) during the first and second trimesters.

UNICEF is working with WHO, the World Bank, the Global Fund for AIDS, Tuberculosis and Malaria, and other Roll Back Malaria partners to support malaria-endemic countries to ensure increased use of insecticide-treated nets, access to effective antimalarial drugs and treatment, and prevention and control of malaria epidemics. During 2003, UNICEF procured >5 million insecticide-treated nets for 25 countries in Africa. Most of the nets were distributed to pregnant women, through antenatal clinics, and to children <5 years of age during routine childhood immunization and measles vaccination campaigns.

Meanwhile, the struggle to curb the spread of HIV/AIDS has benefited from a gradual rise in resources coincident with the effort of WHO, UNICEF, and other partners to place 3 million patients in sub-Saharan Africa into treatment programs by 2005. Moreover, the price of generic antiretroviral drugs has fallen sufficiently for African governments, backed by external resources, to begin prolonging the lives of their citizens.

But in many of the countries of eastern, central, and southern Africa, the AIDS pandemic has already reversed many of the development gains of the last decade—so much so that the Millennium Development Goals the United Nations has targeted for 2015 are already moot. Life expectancy in many countries has dropped from an average 60–62 to age 37–40. Infant death rates in the region are up; children are leaving school to care for sick and dying parents, while whole sectors of society—agriculture, health, education, the private sector—are diminished and compromised by the loss of their most productive workers in what should be the prime of life.

As Stephen Lewis, Special Envoy of the Secretary-General for AIDS in Africa, said recently, "It is an astonishing tribute to the people of Africa—their resilience and their determination—that countries continue to function, heroically, even as they are assaulted by the pandemic." This situation is occurring against a backdrop of immense

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economic and social inequity. The world economy is worth >$30 trillion. Yet nearly half of humanity, 2.8 billion people, most of them women and children, live on ≤$2 a day.

This almost unimaginable impoverishment and lack of employment make the idea of health and health care for women even less attainable. The situation is made worse by high female illiteracy rates in many countries and increasing cuts in government aid for life-saving malaria, HIV/AIDS, and tuberculosis drugs. These factors have led to rampant spread of infectious diseases in the world's poorest communities.

HIV/AIDS is still holding firm as the worst communicable disease in history. The virus is now the leading cause of death in Africa and the fourth leading cause of death worldwide. Africa south of the Sahara has been the worst affected region. Some countries in Asia and eastern Europe are also showing rapid increases in HIV/AIDS prevalence. The fastest rate of infection is among teenage girls. Older men usually infect younger women, either through early marriages for girls or through prostitution.

Any understanding of the gender-based aspects of HIV infection must take into account issues of power, human rights, and social and cultural expectations. A U.N. expert group that met to discuss gender implications of the pandemic concluded that the rapid spread of HIV infection and its deleterious effects on families, communities, and countries were a direct outgrowth of women's inequality and lack of power at all levels.

On the other hand, we know that the active involvement of women and girls in their own well-being is key to bringing about more effective prevention and control of HIV/AIDS. The lack of control by women and girls over their bodies and sex lives, in the context of general socioeconomic subordination, places women all over the world in a more vulnerable situation in relation to HIV/AIDS.

Violence against women is a major risk factor for HIV/AIDS. Infection rates are usually linked to the incidence of rape and other unprotected sexual incidents, especially in times of armed conflict and civil unrest. Women often do not have the power to refuse unwanted sex or to negotiate safe sex with their partners because of fear of violence.

The high death rate among women from HIV/AIDS can be devastating in many countries because of the role women play in child and family survival and community development. Loss of a mother in many parts of the developing world usually means that her young children will die as well, especially those <5 years of age. Orphaned children are most likely to be poorly nourished, miss school, experience emotional trauma, and make themselves more vulnerable to the virus.

Because of this disease, and the social stigma and resulting silence surrounding it, women and children are suffering and dying in ways and in numbers that no earlier generation could have imagined possible. Yet we are confronting a disease that is 100% preventable.

UNICEF has three overarching goals. The first is reducing HIV infection among young people. Our absolute, immutable priority remains the prevention of this disease. And so, in collaboration with young people, U.N. sister agencies, and other partners, UNICEF wants to ensure that every young person has access to basic information on how to avoid infection and that programs are in place to make this information available by 2005. This plan includes access to confidential testing, counseling, and youth-friendly health services that can offer frank information about how sexually active young people can protect themselves and their partners.

Second, we are committed to expanding care and support for orphans and other children made vulnerable by HIV. We need to scale-up alternative forms of care so that such children do not grow up alone, but in familylike environments, with protection, love, and care.

Third, we must reduce mother-to-child transmission. This multifaceted process includes elements of both prevention and treatment. The first step is to prevent infection in women of childbearing age. In some countries, adolescent girls are six times more likely than boys to get infected. This situation is a direct consequence of gender inequality and sexual abuse.

We need to provide women with voluntary and confidential counseling and testing. If they are HIV-positive, they must be given access to antiretroviral drugs to reduce viral loads and chances of infecting their infants. At the same time, they need counseling and advice on feeding options.

Reducing mother-to-child transmission also offers us a foothold in tackling broader treatment, which is both possible and an essential part of the campaign against HIV/AIDS. Success of the immunization campaign, spearheaded by UNICEF and WHO, shows what can be done with antiretroviral drugs in terms of funding, procurement, and distribution.

For now, UNICEF remains convinced that, until an effective medical remedy is found, education is the only effective tool for curbing HIV/AIDS. Only education can empower young people with the knowledge they need to protect themselves and their communities. Only education can combat the discrimination that helps perpetuate the pandemic. And only education can help children and young people acquire the knowledge and develop the skills they need to build a better future, the better future that the international community promised every child a decade ago, at the World Summit for Children. UNICEF is working with governments in more than 161 countries to promote the welfare of children and women. The Millennium

Development Goals, set by the United Nations in 2000, call for reducing the under-5 childhood death rate by two thirds from 1990 to 2015; reducing maternal deaths by three quarters from 1990 to 2015; and reversing the spread and incidence rates of HIV/AIDS, malaria, and other infectious diseases by 2015. Controlling major infectious diseases such as malaria, HIV/AIDS, and others among women and children will be crucial to attaining the key Millennium Development Goals. It is crucial that we work to find ways to improve the socioeconomic status of women, beginning with ensuring their right to education, especially for girls. This effort must also include providing access to clean water and adequate sanitation, health facilities and life-saving drugs, and land and credit as well as promoting women's right to active involvement in the affairs of their community.

Globalization can have a positive impact on children and their families, and its negative effects can be minimized. The challenge is how to bring those benefits, such as new health technologies, to vulnerable groups, especially children, women, and marginalized populations, to prevent and control major infectious diseases such as malaria and HIV/AIDS. The HIV/AIDS pandemic has a woman's face, and if women and girls are not empowered, especially in terms of their own sexuality, the pandemic will never end.

Dr. Bellamy is the executive director of UNICEF. Her interests include immunizing every child; getting all girls and boys into schools that offer quality basic education; reducing the spread of HIV/AIDs and its impact on young people; protecting children from violence and exploitation; and introducing early childhood programs in every country.

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Women, Water Management, and Health

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Women play a major role in domestic water management in areas where safe water and drainage are not available in the house. In these settings, women are typically responsible for collecting, storing, and using water and for disposing of wastewater (1,2). Most studies of women's water management and the health benefits of safe water and sanitation examine the effect of protected water sources, such as covered wells or pumps, and basic sanitation (3). However, water management may also be a health issue in large villages and periurban communities that are supplied with piped water but have inadequate sanitation or drainage facilities. For example, in Egypt's Nile Delta, tap water is available in most rural communities (although not in every house), and no absolute shortage of water exists. However, safely disposing of wastewater and toilet effluent often remains a problem; this problem is exacerbated by the high water table associated with the irrigation system.

We conducted a study on *Schistosoma mansoni* in two Nile Delta villages (each with a population of ≈8,000) from 1991 to 1998. During this period, villagers risked infection with *S. mansoni* when they came into contact with water in irrigation canals; women were especially at risk when washing laundry and utensils in the canal.

In our 1992 survey, both study villages had access to piped water; 78% of households in al-Garda and 39% in al-Salamuniya had household connections. Al-Garda village had a pipeborne sewage system, but only one third of households were connected to it. Although 98% of households in al-Garda and 94% in al-Salamuniya had toilets, many of those households not connected to the sewage system did not safely dispose of effluent. In some cases, effluent in sewage vaults contaminated the subsoil water, and 25% of the toilets in al-Garda and 65% of these in al-Salamuniya had to be emptied periodically, usually with a bucket. A few toilets in both villages illegally emptied directly into a canal or drain. Unsafe disposal of latrine effluent was implicated in schistosomiasis transmission.

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Examining water management in these two villages, we asked what choices women had and why they made decisions that continued to expose them to the risk for schistosomiasis. They found that advice to "Keep away from the canal!" was not relevant to their situation. A number of factors influenced women's water management choices, and hence, their use of the canal: effort involved, water quality and cost, and an appreciation of the opportunity for social interaction with relatives and neighbors.

Women washed domestic utensils and clothes at the canal because it saved them time and effort. If they had no household connection, they had to carry water into the house from a public standpipe. Even in households with an inside tap, women often stored water in case the supply was interrupted. For most women, those who lived in houses without a drainage system, the biggest problem was that all water used in the house had to be carried outside and thrown into the street or canal.

Water quality was also an issue. Women recognized that water from the piped (subsurface) supply was "hard" compared to canal water; in al-Garda, water hardness in the canal measured 210–280 mg/L, compared to 450 mg/L for water from the piped system. Washing at the canal used less soap, and laundry and utensils looked cleaner than if they were washed at home.

A few women said that they used the canal because of the increased cost of water. In the early 1990s, the national water authority was phasing out public standpipes, installing metered connections to every household, and charging for water according to the amount used, rather than a flat rate. Within a few months, the cost of water per cubic meter had risen 250% (4).

Our study suggests that the potential health benefit of piped water supplied to each house is limited if no way to remove wastewater exists. Under recent "cost recovery" policies, poor families may not be able to pay the bills for water, drainage, and sanitation; nor can they pay the full costs required to link up to such systems. Less expensive alternatives are essential; otherwise many households will go without safe drainage and sanitation.

The recent article by Clasen and Cairncross (5) indicates that water management is a high-profile health issue. The authors focus their discussion of the effect of water management on diarrheal diseases. Globally, these kill an estimated 2.5 million people a year, largely among children younger than 5 years (diarrheal diseases are the second most important cause of death among infants in Egypt). The authors do not directly identify water management as a gender issue, but they do point out that epidemiologic studies rarely look at water quality at the point of use. The process of storing and using household water has considerable risk for microbial contamination, even if the water comes from treated, piped sources, and is usually a woman's responsibility (6).

In Egypt, as in poor countries throughout the world, the availability of safe sanitation, especially in rural areas, lags behind that of safe water (7). Epidemiologic studies have indicated that safe sanitation may be even more important than safe water to reduce diarrhea death rates (3). As a health issue, then, safe water and safe sanitation are indissolubly linked.

Three hygiene-related behaviors protect infants against diarrhea: washing hands before preparing food and after using the toilet, safely disposing of infant feces, and safely storing water in the house (5). In Egypt and elsewhere, we need to identify constraints facing rural women that prevent them from adopting these protective behaviors. Identifying barriers to women's adopting certain hygiene, water, and sanitation behaviors could also be important for other health concerns, such as trachoma, recently recognized as resurgent in rural Egypt (8).

These examples suggest that in planning effective control strategies for diseases associated with a lack of safe water and sanitation, we need a greater understanding of women's water management and hygiene behaviors and local constraints they experience. We need to incorporate this knowledge into health promotion, including behavior change. Another issue is women's empowerment, strengthening their ability to make their concerns heard within the community and beyond. Expecting women to change their behavior is unrealistic unless water quality and, especially, drainage and sanitation are upgraded. Policy for safe water and sanitation needs to ensure that water is regularly accessible and safe at the point of use and that sewage and wastewater can be disposed of safely. Above all, a commitment is needed from national governments to provide and maintain safe and affordable water and sanitation for all citizens.

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Conference Session Summaries[1]

Prevention of Mother-to-Child HIV Transmission Internationally[1]

Data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate that in 2003, 34–46 million people were living with HIV infection, and three fourths of these cases were in sub-Saharan Africa. Approximately 2.1–2.9 million children were living with HIV/AIDS. HIV transmission in sub-Saharan Africa is predominately heterosexual, and by the end of 2002, women represented 58% of HIV cases. UNAIDS estimates that in many African countries <1% of pregnant women receive needed antiretroviral prophylaxis to prevent mother-to-child HIV transmission (PMTCT). This has a substantial impact on the death rate in children, with previous gains reversed for children <5 years of age in several countries.

Without intervention, the risk of mother-to-child HIV transmission is 30%–35%. With antenatal HIV testing, combination antiretroviral drugs, and safer infant feeding, the risk can be reduced to 1%–2%. Simplified short-course interventions can reduce PMTCT transmission to 15%-20%. Interventions for PMTCT should also be provided in the broader context of prevention, including primary prevention of HIV, preventing unintended pregnancies, and care and support to HIV-infected women and their families.

U.S. Government Response to Global Mother-to-Child HIV Transmission

In 2002, President George W. Bush introduced the International Mother and Child HIV Prevention Initiative. This initiative was coordinated across several U.S. government agencies including the Centers for Disease Control and Prevention (CDC) and U.S. Agency for International Development. The initiative focused on 14 countries in Africa and the Caribbean with high rates of HIV/AIDS. The goals of the initiative were to reduce mother-to-child transmission by up to 40%; support expanding national PMTCT programs; support linking PMTCT services with antiretroviral treatment and care for mothers, infants, and family members (PMTCT-plus); and reach up to 1 million women annually.

Core interventions include routinely recommending HIV counseling and testing at antenatal clinics, short-course antiretroviral prophylaxis for HIV-positive mother-infant pairs, counseling and support for safe infant feeding practices, and counseling for family planning. Additional interventions include prevention strategies for HIV-negative pregnant women and community mobilization to increase uptake and decrease stigma. By 2003, all 14 countries had started to provide services, and this initiative is now a major activity under the more comprehensive President's Emergency Plan for AIDS Relief, which targets the same 14 countries plus Vietnam.

Implementing PMTCT Programs Internationally

Case Study in Kenya

Kenya has a population of 31.1 million, with 1.2 million births every year. Of the 2.2 million people living with HIV/AIDS in Kenya, 1.4 million are women. The most rapidly growing population becoming infected with HIV is women. HIV-positive women give birth to 118,000 children annually. An estimated 35,000–40,000 of those infants are HIV-positive. Ten percent of reported HIV/AIDS cases in Kenya are in children <5 years of age. PMTCT interventions include antiretroviral drug prophylaxis, optimal obstetric care, infant feeding counseling, and family planning. Replacement feeding (as opposed to breastfeeding) is only recommended in environments where it is acceptable, feasible, sustainable, and safe. Through the CDC Global AIDS Program in Kenya, 18,000 antenatal women have learned their HIV status, and 50% of those who are HIV-positive have received prophylactic antiretroviral drugs. Barriers to testing include a lack of spousal support, fear of partner violence, and fear of disclosure and the stigma that may accompany it.

Case Study in Botswana

Botswana's 2003 surveillance data show that 37.4% of women attending antenatal clinics are HIV-positive. Botswana has had a national PMTCT program since 2001

[1]First authors are session moderators. Remaining authors are listed in order topics were discussed. More session summaries are available at http://www. cdc.gov/ncidod/EID/vol10no11/icwid.htm.

and an expanding antiretroviral treatment program since 2002. Both programs are free to patients. All pregnant women can receive HIV counseling and testing. Antiretroviral prophylaxis for women and infants and infant formula are provided for HIV-positive women. Although 95% of pregnant women attend antenatal clinics and deliver in health facilities, uptake of PMTCT has been low. A CDC-Botswana government survey of pregnant women was performed to explore factors influencing HIV test acceptance. Factors predicting acceptance included higher educational level, attendance at urban clinics, greater knowledge about PMTCT, planned pregnancy, discussing HIV testing with others, and knowing others who had received PMTCT or antiretroviral therapy.

These presentations highlight the successes of PMTCT programs as well as continuing challenges. There continues to be a need for program evaluation, operational research, and expanded PMTCT services in order to maximally prevent mother-to-child HIV transmission.

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Infectious Etiologies of Chronic Diseases: Focus on Women

Infections can directly or indirectly cause chronic conditions through progressive pathology (e.g., chronic infection, inflammation, immunity, malignant transformation), sudden permanent insults (e.g., West Nile virus poliomyelitis paralysis), or by predisposing people to noninfectious sequelae (e.g., neurologic consequences of preterm birth). Bacteria, parasites, prions, viruses, and fungi may be the single or one of several factors contributing to chronic disease; one organism can cause more than one syndrome, and diverse pathogens produce similar syndromes as pathways to disease converge (1). Certain potential outcomes disproportionately affect women (e.g., autoimmune diseases), and in some settings, detection, prevention, or treatment efforts (e.g., ocular trachoma, underdiagnosed genital infections) may marginalize women. Women's activities can also increase exposures to chronic disease pathogens (e.g., schistosomiasis attributable to chores or agriculture), and gender can affect transmission (e.g., increased male-to-female transmission of human T-cell leukemia virus-1). Preventing maternal infections may further minimize chronic disease and neurodevelopmental disorders in offspring.

Are Women's Autoimmune Diseases Really Autoimmune?

Systemic and organ-specific autoimmune diseases, such as rheumatoid arthritis and myocarditis, are the leading cause of death in women >65 years of age (2). They affect 14–22 million people (5%–8% of the population) in the United States (3) and millions more worldwide. In autoimmunity, the immune system may attack or damage self-tissues with autoantibodies and autoreactive T and B cells. However, the indolent nature of most autoimmune diseases makes determining infectious triggers difficult. Animal models help to understand such links. For example, transfer of disease by autoantibodies and immune cells from affected animals indicates the immune-mediated nature of these syndromes (4–6). Toll-like receptors and the innate immune system, critical components of the normal human response to infection, are essential to naturally and experimentally induced autoimmunity. Genetic and other factors affect susceptibility to both infection and autoimmune disease. For example, coxsackievirus B3 induces viral myocarditis in susceptible mice. Certain cytokines (interleukin [IL]-1 and tumor necrosis factor [TNF]-α), but not viral replication, correlate with cardiac inflammation and can overcome resistance to chronic myocarditis (7–9). These findings suggest that, while infection may trigger autoimmunity, immune processes drive disease progression. Estrogen amplifies the immune response to coxsackievirus B3 in susceptible mice, increasing TNF-α and IL-4 levels (unpub. data), which is perhaps consistent with women's predisposition to autoimmune disease. Identifying triggers, including infection, and early markers of autoimmunity are important goals for preventing onset of or disrupting progression to autoimmune disease.

Infection Connection in Neurodevelopmental Disorders

Intrauterine infections are known causes of congenital defects worldwide. Infections during the time of fetal brain development might also contribute to neuropsychiatric disorders, including schizophrenia. Studies linking various gestational insults (including infections) and subtle premorbid behavioral alterations to adult schizophrenia implicate a neurodevelopmental origin. However, the long

latency between putative infection or insult and the emergence of psychotic symptoms complicates establishing direct links. While most reports have been ecologic studies without confirmed maternal infection, Brown et al. (10) found that 20.4% of persons with a documented in utero exposure to rubella developed an adult schizophrenia spectrum disorder. Experimentally, lymphocytic choriomeningitis virus infection in a neonatal rat model produces some latent changes similar to those of schizophrenia, e.g., hippocampal atrophy and impaired inhibitory GABA neurotransmission (11); blocking IL-1 partially attenuates the hippocampal cell loss. Inflammatory cytokine responses, perhaps amplified by immunogenetic abnormalities, may be a common thread linking intrapartum infections and noninfectious gestational and obstetric complications to neurodevelopmental disorders (12).

Keys to the Future

A continuum from acute infection to chronic disease exists, and each stage is an opportunity to prevent or minimize an avoidable fraction of chronic disease– that resulting from infectious disease. Crucial steps include identifying infectious etiologies and cofactors, determining persons (including women) at risk for infection or outcome, and implementing measures that minimize chronic sequelae. Research incorporating longitudinal studies that precede clinical disease must support evidenced-based conclusions and actions. The benefits to women could be substantial.

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Disproportionate Impact of Sexually Transmitted Diseases on Women

Worldwide, sexually transmitted diseases (STDs) and HIV affect women more than men. This gender differential is greater in developing countries than in industrialized countries, and biological, social, cultural, and economic factors all contribute to the gender differential in STD/HIV. Larger mucosal surface area, microlesions caused during sex (particularly forced sex), and the presence of more HIV in semen than in vaginal secretions all contribute to women's greater vulnerability to STDs and HIV.

Their sex partners' behaviors also put women at risk for STDs and HIV. Culturally, men are expected to have multiple sex partners, including sex workers, and women may risk abuse or suspicion of infidelity if they refuse sex or request protection. Financial and material dependence on men renders women economically more vulnerable to STDs and HIV. Often women are under pressure to find a husband or bring home money, which in the absence of viable alternatives leads them into sex work. Effective prevention of STDs and HIV necessitates large-scale social,

cultural, and economic changes and female-controlled prevention, such as microbicides.

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Impact of HIV on Women in the United States

In the United States, AIDS was first reported in women in 1981 (1), and the percentage of AIDS cases in women has continued to increase, accounting for an estimated 26% of new AIDS diagnoses in 2002 (2). Since 1998, deaths among women with AIDS in the United States have remained stable at an estimated 4,000 (2).

Epidemiologic Features of HIV in Women, United States

Data from 29 states with confidential name-based HIV reporting since 1998 were used to describe the status of HIV disease among women from 1999 through 2002. HIV diagnoses were defined as diagnoses of HIV infection regardless of AIDS diagnosis status. This diagnosis includes persons with a diagnosis of HIV infection only, HIV infection and later AIDS diagnosis, or concurrent diagnoses of HIV infection and AIDS.

From 1999 through 2002, an estimated 101,872 HIV diagnoses were reported from 29 states: 72,007 (70.7%) in men and 29,865 (29.3%) in women. Among women, 71.9% were non-Hispanic blacks, 18.2% were non-Hispanic whites, 8.4% were Hispanics, 0.6% were American Indian/Alaska Natives, and 0.4% were Asian/Pacific Islanders. The two principal modes of HIV exposure for women were heterosexual contact and injection drug use, accounting for 77.7% and 20.5% of diagnoses among women, respectively. Women were diagnosed with HIV at younger ages than men. For the 4-year period, 31.3% of women with HIV were in the 13- to 29-year age group compared with 19.9% of men in the same age group. HIV diagnosis rates were consistently higher among non-Hispanic black women compared with women from other racial and ethnic groups for all 4 years.

Prevention Strategies for Women

In 2003, the Centers for Disease Control and Prevention (CDC) introduced the Advancing HIV Prevention (AHP) initiative (3). AHP aims to reduce barriers to early diagnosis of HIV infection, increase access to quality medical care and treatment, and provide ongoing prevention services for persons living with HIV. AHP incorporates four priority strategies: make voluntary HIV testing a routine part of medical care, implement new models for diagnosing HIV infections outside of the medical settings, prevent new infections by working with persons diagnosed with HIV and their partners, and decrease perinatal transmission.

Clinical Care of Women with HIV

HIV-infected women may be at increased risk for medical problems and metabolic changes. Studies have shown that HIV-positive women were more likely to develop genital warts and cervical intraepithelial neoplasia (4) and were at increased risk for viral infections (5). According to one study, HIV-positive women were 80% more likely to be anemic than HIV-positive men (6). Compared with HIV-negative controls, women with HIV were more likely to have elevated triglycerides and insulin levels (7) and decreased bone mineral density (8).

Determining when to initiate antiretroviral therapy for HIV-infected women is based on CD4+ T cell count (9). Because no gender difference exists for initiating or applying antiretroviral drug regimens, the guidelines for treating women are the same as those for treating men. Overall, drug efficacy does not differ by gender in randomized clinical trials.

For many reasons, women with HIV may avoid HIV testing and care. Often, women may be stigmatized and endure discrimination because of their HIV status. Women are often the primary caregivers for other family members, which may lead to avoiding or delaying testing and care. Economic dependence on a spouse or significant other may also play a role in whether a woman seeks testing and care. Mistrust of the healthcare system may also exist. Depression or domestic violence may also affect a woman's ability to seek needed care for HIV infection.

Incorporating HIV Prevention into Medical Care

In 2003, CDC, the Health Resources and Services Administration, National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America issued recommendations to assist clinicians in integrating HIV prevention into primary care for HIV-infected persons. Providers are encouraged to deliver brief prevention messages during primary care visits, screen for HIV risk behaviors and sexually transmitted disease, pro-

vide HIV behavioral risk-reduction messages, and facilitate partner notification and counseling (10).

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Human Papillomavirus and Cervical Cancer

Though cervical cancer is highly curable when detected early, it remains one of the leading causes of cancer death in women worldwide. Early detection is effective because the precursor lesions evolve slowly into invasive cancer, typically over a period of >10 years. These precursor lesions (dysplasias or cervical intraepithelial neoplasias [CIN]) are detected with cervical cytology screening, the Pap smear. In every country where a Pap smear screening program has been introduced, rates of cervical cancer have been substantially reduced. The discovery that human papillomaviruses (HPV) are etiologically linked with cervical cancer has led to efforts to apply this knowledge to improve cervical cancer screening and to potentially prevent cervical cancer through vaccination.

HPV and Cervical Cancer

HPV is not a single virus but a family of closely related viruses, each designated as a type, numbered in order of discovery. Typing is based on nucleic acid sequencing. More than 100 HPV types are known to exist, and at least 30 can be detected in the anogenital tract. No simple in vitro culture methods are available for identifying it, and serologic testing is insensitive. Techniques for identifying the virus are based on nucleic acid detection, either direct hybridization or after amplification. HPV types associated with malignancies are referred to as high-risk types, and those associated with warts (condylomas) are rarely found in cancers and are called low-risk types.

Sexual transmission is the dominant mechanism for acquiring genital HPV. Infection is usually transient and not associated with symptoms. An estimated 80% of sexually active women have been exposed. Studies have detected HPV in 90% of cancers worldwide, and plausible biologic mechanisms can explain oncogenesis. The magnitude of the risk association between HPV and cervical cancer is greater than that for smoking and lung cancer. However, infection alone is insufficient to cause cancer, and additional factors are required for neoplasia.

HPV Vaccination as a Prevention Strategy

One investigational quadrivalent vaccine includes types 6, 11, 16, and 18. HPV-16 and HPV-18 (high-risk types) are found in 25% of all CIN I lesions and 70% of CIN II/III and anogenital cancers. HPV-6 and HPV-11 (low-risk types) are found in 25% of CIN I lesions and 90% of anogenital warts. Therefore a prophylactic vaccine against these four types would substantially reduce HPV-related disease.

Vaccine candidates have been evaluated in animal models of papillomavirus infection. The L1 protein of HPV is

the major capsid protein and self-assembles into viruslike particles (VLPs). Species-specific VLP vaccines provide protection against infection and disease. Protection was associated with the development of neutralizing antibodies. Serum from vaccinated animals conferred protection to unvaccinated animals.

The HPV-6, HPV-11, HPV-16, and HPV-18 L1 VLP vaccine is manufactured in *Saccharomyces cerevisiae* (yeast), and yeast-derived vaccines have been given to millions of children and adults. The vaccine includes amorphous aluminum hydroxyphosphate sulfate adjuvant and is given in a 0-, 2-, 6-month dosing scheme. Phase I trials (300 participants) were performed to establish immunogenicity and tolerability of a range of doses of monovalent HPV L1 vaccines. Phase II trials (3,500 participants) were performed to establish the immunogenicity and tolerability of a range of HPV L1 VLP vaccine dose formulations and provide preliminary proof of concept. Phase III trials (20,000 participants) will determine the efficacy of the HPV L1 VLP vaccine by using prevention of type-related CIN I, genital warts, and CIN II/III as the endpoints.

The results of the phase II trial of the HPV-16 VLP vaccine have been recently published (1). The primary endpoint of this trial in 2,392 young women was persistent HPV-16 infection (detection in consecutive visits) and HPV-16-related CIN. In 16- to 23-year-old women who were HPV-16-naïve at baseline, the vaccine was 100% effective; HPV-16 and CIN were detected in 41 unvaccinated (placebo) women and in no vaccinated women. The vaccine was generally well tolerated, and no serious vaccine-related adverse events were seen.

The phase III efficacy trial addressing women 16–-23 years is underway. Approximately 25,000 women in 33 countries and 100 sites have been enrolled. The evaluation includes Pap testing and HPV polymerase chain reaction at defined intervals. An adolescent program (for girls 9-15 years of age) is ongoing to demonstrate vaccine immunogenicity and tolerability in boys and girls. In addition, a study with Nordic Cancer Registries is planned for long-term (>10 years) follow-up postlicensure to determine duration of efficacy, long-term safety, and replacement of vaccine types with other HPVs. Phase III programs will definitively evaluate clinical and public health impact of the HPV vaccine in adolescents and adult women.

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Impact of HIV on Women Internationally

Women bear about half of the HIV infections worldwide. In sub-Saharan Africa, 58% of those infected are women; in Asia this figure is 30%. While the epidemic occurs in varied geographic regions, all women are biologically and socioculturally vulnerable.

Our common prevention options fail to take into account women's realities: being in, or wanting to be in, a union; wanting to have children; the imbalance of power in male/female relationships; inaccessibility of education; the threat of sexual violence; and the economic vulnerability that leads to engaging in sexual activity for survival. Female-controlled methods, including female condoms and microbicides, are essential and must take into account these realities. The prevention needs of women already infected with HIV must be addressed by supporting disclosure, fighting stigma, and being sensitive to the threat of violence and disinheritance.

The burden of care for those living with HIV/AIDS most often falls to women and girls. Recognition of the value of this work is vital, as is addressing practical issues that can help alleviate this burden of care.

HIV-Positive Women's Perspective, Advocacy, Sexual and Reproductive Rights

Biomedical, social, and human rights factors are compelling reasons for giving particular attention to women and HIV. However, research on women and HIV/AIDS in terms of treatment, adherence, and opportunistic infections is deficient. Women lack access to treatment, and women's representation in treatment advocacy initiatives remains wanting.

In terms of sexual and reproductive health, women face barriers in accessing treatment for sexually transmitted infections and have inadequate access to prophylactic treatments such as Pap smears and sexual health screenings. Female condoms are often unobtainable, and accelerated research on woman-controlled barriers is needed. Many programs for HIV-positive women lack services to support safe conception, frequently consider women only or primarily in terms of reproduction, and can unethically deny HIV-positive women reproductive health services.

Scientific research, programs, and initiatives should focus on HIV-positive women and their interrelation with treatment, adherence, opportunistic infections, female-

controlled prevention methods, and reproductive health. These findings must then be translated into ethical policy and practice.

HIV among Young Women in Developing Countries

Youths (persons 15–24 years of age) are a major part of the HIV epidemic around the world, making up an estimated half of new HIV infections, and young women are typically infected earlier than are men. Young women have both biological and social vulnerabilities. They can be susceptible to "sugar daddy" relationships, they are vulnerable to sex trafficking or coercion, and they have less education, including HIV prevention education, than their male counterparts. Some countries have had success in reducing HIV among young women; however, many program challenges remain: lack of evaluation, limited resources, the unique vulnerabilities of youth ignored, and the lack of influence by young persons.

Fifteen million children 15 years of age and younger have lost one or both parents to AIDS, and this situation also presents challenges, including increased risk of sexual exploitation, the loss of educational opportunities as young people are forced to leave school because they lack school funds or must work to support remaining family members, and the need for HIV prevention education that addresses orphans' special needs.

Some promising youth programs have been initiated, among them curriculum-based programs, peer education, and voluntary counseling and testing; however, more resources and evaluation must be devoted to youth programs, and these programs should view youth as assets, not as problems.

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Hepatitis B in Women: Domestically and Internationally

Globally, hepatitis B virus (HBV) infection is a major cause of infectious disease-related death, causing approximately 620,000 deaths annually. Without hepatitis B vaccination, an estimated 1.4 million HBV-related deaths would occur in the 2000 birth cohort over the lifetime of the cohort. HBV infections acquired in the perinatal and early childhood periods account for 21% and 48%, respectively, of HBV-related deaths worldwide. Thus, routine vaccination of infants and children serves as the basis for a global hepatitis B prevention program.

In 1992, the World Health Organization recommended that hepatitis B vaccine be included in childhood immunization programs in all countries, but because of financial constraints, many countries were unable to initially implement this recommendation. In 1999, a global initiative began to make hepatitis B vaccine available to children living in 69 of the world's poorest countries, and by the end of 2003, routine childhood hepatitis B vaccination was included in national immunization programs in >151 countries. However, many countries, mainly in sub-Saharan Africa, have not yet introduced the vaccine, and coverage with the three-dose vaccination series remains low in many countries that have introduced the vaccine. When all countries have introduced the vaccine and coverage with the three-dose vaccination series reaches 90%, up to 84% of global HBV-related deaths will be prevented.

Hepatitis B in the United States

In the United States, an estimated 5% of the civilian, noninstitutionalized population has serologic evidence of past or present HBV infection, and 0.4%-0.5% have chronic infection and are the primary source of infection for others. From 1990 through 2002, the incidence of reported acute hepatitis B declined 67%. The incidence of acute hepatitis B among men has been consistently higher than among women. In 1990, the incidence among men and women was 9.8 and 6.3 per 100,000, respectively; in 2002, the incidence was 3.7 and 2.2 per 100,000, respectively. Overall, incidence among women has declined more than among men. Trends in acute hepatitis B reflect poor vaccination coverage among persons who engage in high-risk behavior.

Persons at high risk for HBV infection often seek health care in settings in which vaccination services could be provided. During 1996–1998, approximately half of persons with reported acute hepatitis B previously had been treated for a sexually transmitted disease (STD) or incarcerated: 89% of injection drug users, 35% of men who have sex

with men, and 70% of persons with multiple sex partners with reported acute hepatitis B had been previously incarcerated or treated for an STD. Both STD clinics and correctional facilities are settings in which hepatitis B vaccination services are recommended.

Programmatic Success in High Risk Settings

In August 1999, Denver Public Health (DPH) began offering hepatitis B vaccine to adults at high risk in the public STD clinic. Initial funding for the vaccine was first allocated by the Denver City Council. Patients were asked if they had a history of hepatitis B vaccination or disease and questioned about risk behavior; no serologic screening was done. The selective vaccination process was cumbersome, and clinicians required frequent reminders to implement it. Of clients seen in the STD clinic, 58% accepted the vaccine and were directed to receive it in the immunization clinic in the same building. Of clients who agreed to the free vaccine, 29% left before receiving it. Procedures changed when additional funding was secured in January 2002. Client selection was discontinued, and all clients of the STD and HIV Counseling and Testing clinics were offered vaccine, which increased its initial acceptance to 77%. Vaccination rates were further improved by having personnel available to vaccinate clients on site, before they left the clinic.

DPH used a vaccine registry, adapted from one implemented to track pediatric vaccinations, to assess clients' vaccination status before doses were given. The results indicated that clients were not differentiating between vaccinations and various other tests or medications in self-reporting of immunization status. Use of the vaccine registry was crucial for evaluating completion rates and eliminating revaccination of persons already immunized.

A highly successful hepatitis B vaccination program can be established within another public health infrastructure. The process requires commitment from all involved programs because changes in service delivery are needed to accommodate vaccination. The largest issue confronting programs is continued funding for vaccine.

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Refugees, Forced Displacement, and War

Women make up high proportions of refugee and internally displaced populations, and they suffer unique consequences of war and conflict because of gender-based violence, discrimination, and caretaking roles. Refugee women are especially vulnerable to infectious disease, as well as threats to their mental health and physical safety.

Infectious Causes of Maternal Death in Refugee Populations in Afghanistan

The Reproductive Age Mortality Survey (RAMOS) in Afghanistan consisted of death identification followed by death investigation. The study identified 357 deaths of women of reproductive age (15–49 years) among residents of 16,000 Afghani households and investigated 80% of these deaths through the verbal autopsy method. The maternal death rate is extremely high (1,600–2,200 deaths per 100,000 live births) in Afghanistan as a whole, and the estimate in one study site was the highest ever recorded (6,500/100,000 live births in Ragh, Badakshan). The vast majority of maternal deaths were attributed to direct obstetric causes. Infectious causes, primarily tuberculosis, malaria, and postpartum sepsis, accounted for 12% of deaths. Tetanus, tuberculosis, and malaria often claimed women's lives while they were pregnant.

Women faced substantial barriers to care, and very few accessed preventive or curative services. In a country of very low resources and conflict such as Afghanistan, policy development and program implementation to reduce maternal deaths are challenging. Causes of maternal death are multifactorial and cannot be resolved simply by increasing the percentage of deliveries by skilled birth attendants. Infectious causes of death identified in this study illustrate the need for comprehensive maternity care, including preconceptional, prenatal, and postnatal care, integrated with other reproductive health and primary care services.

Impact of War on Women's Health: Refugees from Liberia and Sierra Leone in Nigeria

A study carried out between January and March 2004 with Liberian refugee women residing in the United Nations refugee camp at Oru village in Ogun State, Nigeria, shows how forced migration contributes to increased incidence of both communicable and noncommunicable diseases in women. Liberia's civil war resulted in approximately 215,000 refugees at the end of 2001; 50% to 80% of these refugees were women. During the civil war, an estimated 40% of all Liberian women were raped. Loss of family forces women to depend on men and may lead to rape, forced marriage, prostitution, domestic

abuse, and increasing risk of HIV and other sexually transmitted infections. Lack of postwar shelter compounds other problems and increases exposure to mosquitoborne diseases. Lack of clean drinking water introduces risks of bacillary dysentery, cholera, diarrheal disease, typhoid, hepatitis A, and other diseases.

Researchers concluded that solutions to the negative impact of war on women's health should be based in education, empowerment, efficient publicity, and effective policies. A sub-ministry devoted to women's affairs and maternal and child health was recommended, with funding specifically earmarked for women's health. Regular screening for preventable or treatable disease should be done in the home country and continued after the safety period ends.

Violations of International Women's Rights: Effects on the Overall Health of Women

Findings from a study by Physicians for Human Rights indicate that nearly half of all households in three southern cities in Iraq experienced human rights abuses among household members between 1991 and 2003. Such abuses represent considerable challenges for justice and accountability and emphasize the need to address individual and community mental health needs on a large scale. The prevalence of mental illness represents a challenge to the Iraqi health system, since <100 psychiatrists are reported to practice in the country, and therapeutic medications and social support systems are lacking.

Households surveyed expressed support for a government that would protect and promote human rights, including the rights of women. However, the lack of support for certain women's rights by both men and women may make the full range of women's human rights difficult to achieve. Consequently, restrictions on women's rights or ineffective representation of women may have substantial, adverse health consequences for women and girls. This study suggests the need for a gender- and rights-based approach for reconstruction and community health and development in Iraq.

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Prevention of Hepatitis C in Women

Hepatitis C is a major public health problem in the United States. Although the incidence of new infections declined substantially in the past decade, approximately 25,000 persons are infected each year. In total, an estimated 2.7 million Americans have chronic hepatitis C virus (HCV) infection and are at risk for HCV-related chronic liver disease and hepatocellular carcinoma (HCC).

The most common exposure associated with HCV infection is use of injection drugs. Other less commonly identified risk factors include sexual contact; transfusions before blood screening was implemented; and occupational, nosocomial, and perinatal exposures. Although sources of HCV infection are the same for men and women, the overall prevalence of HCV infection is lower among women than men, which is likely related to the lower prevalence of injection-drug use among women.

The risk for HCV transmission from mother to infant is about 5%–6%; transmission occurs only from women who are HCV RNA positive and is higher among those coinfected with HIV (≈18.7%) than among women not infected with HIV (≈5.4%). The influence of factors such as maternal viral titer and interventions at the time of delivery is unclear. Studies indicate that breastfeeding is not a risk factor for perinatal transmission.

Most hepatitis C prevention strategies are gender neutral and include screening and testing donors of blood, plasma, organ, tissue, and semen; virus inactivation of plasma-derived products; effective infection control practices; identification, counseling, and testing of at-risk persons; and medical management of infected persons. Pregnant women with risk factors for infection should be identified, screened, and counseled regarding the risk for perinatal transmission.

Clinical Reports

Although risk factors for HCV acquisition are similar among men and women, women are at higher risk of acquiring HCV from sexual contact with an HCV-infected partner and more likely to be initiated into drug use, share needles, or be injected by a sexual partner. Among HCV-infected women, pregnancy may lead to worsening of histologic disease. Other gender differences in the natural history of hepatitis C are that the rate of spontaneous HCV clearance may be higher among women than men, the risk for fibrosis progression and HCC are lower in women than men, and alcohol use by women with hepatitis C is likely to have more pronounced negative effects on the liver than is observed among HCV-infected men. There do not appear to be substantial gender differences in response to currently available therapy.

International Perspective

Approximately 2.2% of the world's population, 130 million people, are infected with HCV. Worldwide, an estimated 325,000 deaths from HCV-attributable HCC and cirrhosis occur annually. In industrialized countries, most HCV-infected persons have prevalent, chronic infections, attributable to past exposures such as injection drug use, blood transfusions, and sexual contact. Primary prevention strategies include reducing harm and preventing nosocomial transmission. In developing countries, many incident, new infections are due to health care-related exposures such as unsafe injections, and prevention strategies focus on safe health care as well as reducing harm.

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International Conference on Emerging Infectious Diseases

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Approximately 2,100 scientists and public health officials from the United States and 64 other countries gathered in Atlanta, Georgia, February 29 – March 3, 2004, for the fourth biennial International Conference on Emerging Infectious Diseases. The aims of the conference were to present the latest scientific information from a variety of disciplines on the new and emerging microbial threats to public health around the world and to encourage and enhance the partnerships that are critical to addressing them. The conference was sponsored by the Centers for Disease Control and Prevention, the American Society for Microbiology, the Association of Public Health Laboratories, the Council of State and Territorial Epidemiologists, and the World Health Organization, as well as 38 partner organizations. The scientific program committee had representatives from 23 agencies and organizations.

The field of infectious diseases is fast-moving, as new challenges around the world engage the efforts of physicians, epidemiologists, microbiologists, veterinarians, and social scientists to understand them well enough to control and prevent them. Meeting these new challenges, with the best science and with the most effective policies, was the continuing theme of this multidisciplinary conference. The conference schedule was built around 12 plenary speakers and 16 panels of invited talks, along with 115 scientific oral presentations and 345 posters, chosen from 711 submitted abstracts. Four lunchtime sessions were devoted to discussing practical aspects of emergency response, such as the extensive experience with quarantine in the severe acute respiratory syndrome (SARS) epidemic. Six breakfast "meet-the-network" sessions introduced some of the current international surveillance and response networks. The International Conference on Women and Infectious Disease and other satellite meetings provided time for discussion and amplification of the interlocking issues and relationships.

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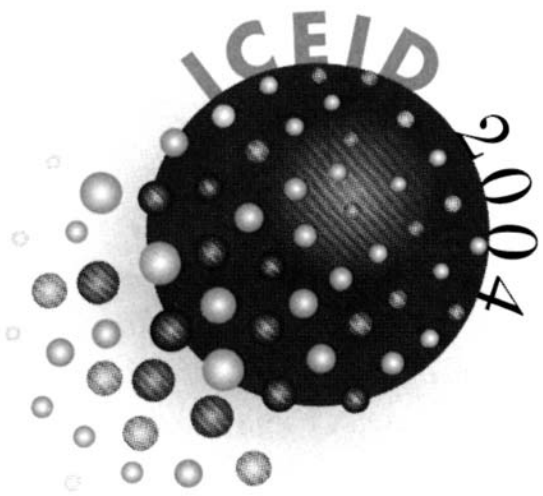
The opening session outlined the central themes of the conference, with addresses by Julie Gerberding, director of the Centers for Disease Control and Prevention (CDC) and administrator of the Agency for Toxic Substances and Disease Registry; David Heymann, representing the director-general of the World Health Organization; William Sergeant, chairman of Rotary International's International PolioPlus Committee; and James Hughes, director of CDC's National Center for Infectious Diseases. The central themes they introduced recurred through many of the presentations. New pathogens, new antimicrobial resistance, and new routes of transmission continue to emerge as public health challenges. Many emerging pathogens are global, move swiftly from continent to continent, and cross readily from animal reservoirs to humans. Mounting an effective public health response depends on international collaboration across continents, cultures, and disciplines. Shaping effective mechanisms for control and prevention is the collective and exciting work of public health in the coming decade.

The conference also featured new information and major advances in understanding the latest global concerns, such as SARS, West Nile virus, avian influenza, and increasing antimicrobial resistance problems in many



pathogens. The transformations of the developing world, with new patterns of consumption and leisure, are creating opportunities for the emergence of pathogens, at the same time as growing regional and international networks are evolving to better understand and monitor them. In many places, preparations to meet the threat of biocrime or bioterror are strengthening the capacity of public health systems to respond to future natural threats of pandemic and panzootic disease.

The conveners summarized presentations from each of the invited panels devoted to specific topics; some of these are published in this issue of Emerging Infectious Diseases. A tribute given at the conference to the late Robert Shope, a distinguished arbovirologist, has appeared in the journal (1). Planning has already begun on the fifth International Conference on Emerging Infectious Diseases, to be held in March 2006 in Atlanta.

Acknowledgments

We are deeply grateful for the commitment and hard work of the scientific and administrative committees.

Dr. Tauxe is a medical epidemiologist, chief of the Foodborne and Diarrheal Diseases Branch, National Center for Infectious Diseases, CDC. His public health research focuses on improving surveillance, investigation, control, and prevention of bacterial enteric infections.

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Plagues, Public Health, and Politics[1]

Jeffrey P. Koplan* and Melissa McPheeters*

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On July 1, 1665, the lord mayor and aldermen of the city of London put into place a set of orders "concerning the infection of the plague," which was then sweeping through the population. He intended that these actions would be "very expedient for preventing and avoiding of infection of sickness" (1).

At that time, London faced a public health crisis, with an inadequate scientific base in that the role of rats and their fleas in disease transmission was unknown. Nonetheless, this crisis was faced with good intentions by the top medical and political figures of the community.

Daniel Defoe made an observation that could apply to many public health interventions then and today, "This shutting up of houses was at first counted a very cruel and unchristian method… but it was a public good that justified a private mischief" (1). Then, just as today, a complex relationship existed between the science of public health and the practice of public health and politics. We address the relationship between science, public health, and politics, with a particular emphasis on infectious diseases.

Science, public health, and politics are not only compatible, but all three are necessary to improve the public's health. The progress of each area of public health is related to the strength of the other areas. The effect of politics in public health becomes dangerous when policy is dictated by ideology. Policy is also threatened when it is solely determined by science, devoid of considerations of social condition, culture, economics, and public will.

When using the word "politics," we refer not simply to partisan politics but to the broader set of policies and systems. Although ideology is used in many different ways, in this case, it refers to individual systems of belief that may color a person's attitudes and actions and that are not necessarily based on scientific evidence (2).

Public Health Achievements

Science influences public health decisions and conclusions, and politics delivers its programs and messages. This pattern is obvious in many of public health's greatest triumphs of the 20th century, 10 of which were chronicled in 1999 by the Centers for Disease Control and Prevention (CDC) as great public health achievements, and several of which are presented below as examples of policy affecting successes (3). These achievements remind us of what can be accomplished when innovation, persistence, and luck converge, along with political will and public policy.

Vaccination

Childhood vaccinations have largely eliminated once-common, terrible diseases, such as polio, diphtheria, measles, mumps, and pertussis (4). Polio is being eradicated worldwide. The current collaboration between the World Health Organization, the United Nations Children's Fund, CDC, and Rotary International is a political as well as biological "tour de force," and eradication of polio in Nigeria has been threatened by local political struggles and decisions. In the United States, politics has contributed to successful public health policies by requiring vaccination at school entry, which has been vital to achieving high vaccine coverage in young children.

Debate about vaccines offers an example of the effect of ideology on public health progress in the form of persons who oppose vaccination. These persons put communities at risk by refusing vaccination for themselves and their children and enlist political support to undermine our greatest medical advance.

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[1]Presented initially on March 2, 2004, at the Fourth International Conference on Emerging Infectious Diseases, Atlanta, Georgia, USA.

Family Planning

Safe contraception and family planning have not only improved the health of women by preventing unintended pregnancies, but they have also contributed to one of the century's most dramatic social revolutions by helping redefine roles and opportunities for women (5). However, ideologic views on contraceptive practices and sexually transmitted disease (STD) prevention continue to contradict scientific observations, which leads to compromised public health policies.

Control of Infectious Diseases

Clean water, treated to protect us from outbreaks of infections like cryptosporidiosis, is an obvious example of the interaction between public policy and infectious disease control. Public policy has sought to control infectious disease throughout history, including attempts to ban spitting in the streets around the turn of the century (an issue that resurfaced 100 years later in the context of severe acute respiratory syndrome [SARS]) and imposing restaurant inspections to ensure sanitary conditions in food preparation. Many important infectious disease issues have political and economic overtones: Legionnaires' disease and hotel closures, Nipah virus outbreaks and the swine industry, hantavirus and the cultural and political interplay with Native American communities, and drug resistance and inappropriate and widespread antimicrobial drug use in the food industry and medicine are just a few examples (6).

Recognizing Tobacco Use as a Health Hazard

Knowing that tobacco is addictive and dangerous alone did not ensure that tobacco companies were held responsible for their role in impairing many people's health. Rather, that accomplishment required a combination of political will and social insistence (7). Nonetheless, regulations on secondhand smoke continue to be debated, as science and individual ideology clash. These clashes become especially acrimonious as they reflect culture around a native-grown substance and often the product on which a state's economy has depended.

New Challenges

In just the past 2 years, new health challenges have occurred that illustrate the tension between economic health of a community or a business and the personal health of citizens or employees, for example, or the role of the individual versus the government in taking responsibility for health and health-related actions. In emerging infectious diseases, these new health challenges include avian flu and bovine spongiform encephalopathy, as well as SARS.

What makes infectious diseases particularly compelling to the public, to public health and political involvement, is that microbial agents are frightening. They come from exotic places, jump from person to person, often have no treatments or preventive measures available, and can paralyze industries and communities. Infectious agents represent our lack of control over our health, regardless of whether they are used deliberately by terrorists or are delivered by nature. Many infectious diseases have become a security issue, bringing a new set of "partners" to the microbiologic and public health table. While this arrangement is appropriate and necessary in many instances, it also has potential for abuse, by promoting anxiety and insecurity for political means, distorting public health priorities, and possibly militarizing public health institutions.

Smallpox

The decision to implement widespread vaccination against smallpox generated substantial interest in the general public. After believing that smallpox was not a threat for many years, we were informed by the government that cause for serious alarm existed.

Production of large quantities of vaccine was accelerated, which was a prudent and decisive action. This action was followed by a policy that called for vaccinations for hundreds of thousands of healthcare workers and millions of first responders. The science on which this decision was based seemed shaky at best, and many chose to forego vaccination, including two distinguished academic infectious disease units. The Washington Post criticized these units, saying, "There are reasons, moral and medical, to deplore the decision of those doctors who refuse in this manner…. Their job is not to assess intelligence risks or to second-guess state public health officials but to be prepared to care for sick people, and to vaccinate healthy people" (8).

The Post's statement may be correct, but academic infectious disease specialists have every right and responsibility to question decision-making that affects their patients and colleagues, especially when the scientific-political interface regarding that decision is unclear. Careful review of the literature and expert experience predicted substantial risks from adverse vaccination reactions.

The Washington Post editors seem to have missed the concept of "do no harm." Analytic and compassionate physicians realized that, in the face of little or no threat of an attack, widespread use of a potentially toxic vaccine was not in the best interest of their patients. The decision by various academic medical centers not to widely vaccinate hospital and medical personnel seems prudent, given the revised estimates of risk and the reporting of substantial adverse reactions.

Bioterrorism is not the only infectious disease challenge with political implications. Existing pathogens and newly emerging diseases remind us that infectious agents can destabilize our social structure and commerce, and

they may require political or policy intervention. Therefore, the danger is that ideologic stances may intrude on the process and push us away from science and even away from good public health practice.

SARS

The SARS outbreak in Asia in 2003 provided examples of how ideology and politics can interfere with public health practices and bring criticism by ideologues. Moreover, SARS demonstrated the challenge of protecting the public's health across national and ideologic lines. The SARS outbreak was not reported by the Chinese government for the first several months of its transmission (9). An ideologic perspective that required not sharing weaknesses or inadequacies with the rest of the world probably played a role in this delay. The political pressure of the rest of the world was required to convince China to acknowledge the problem and accept help.

Hong Kong, on the other hand, was more open. Early cases of atypical pneumonia were identified and reported. Further cases were ascertained, and contact tracing was put in place. The system responded with infection control efforts, including isolation and quarantine. Nonetheless, Hong Kong faced a daunting task, with a high population density and a poorly understood disease. In the end, Hong Kong's department of health faced substantial criticism from political opposition and the press, and a committee was formed to evaluate their response. The committee developed a number of recommendations but recognized overall the impressive response of the hardworking public health and healthcare communities (10). Nonetheless, persons initially critical of the response itself took the opportunity to criticize the report by an international panel. Certainly, being critical and trying to improve performance are valuable, but are they best done in the middle of the challenge and with blatant political intent?

2003–2004 Flu Season

For influenza, the scientific and political processes need to be improved. For many years in public health, we have recognized the threat of pandemic flu and called for the need to act (11). In this case, politics is more than helpful, it is essential. Preventing a flu pandemic necessitates using the resources of science, politics, and the private sector. Last year, vaccine development became a matter of public concern when several children died from influenza early in the season, and the press reported that the vaccine may have lacked protection against the circulating Fujian strain.

Public discussions highlighted the imperfections of science, particularly related to vaccine production and distribution. Then the finding of cases of H5N1 influenza in Asian chicken flocks and other birds and several human infections and deaths rekindled apprehension about a flu pandemic with a new, lethal strain, should mutations permit person-to-person transmission. With avian flu, some government officials were slow to disclose infected flocks to protect economic interests, and these decisions could have had tremendous potential health effects around the world. Thus politics continues to influence infectious disease control on micro and macro levels.

Ideology and Science

Early in the HIV/AIDS epidemic, the ideologies of scientists, clinicians, and politicians worked against one another as they affected decisions about paying attention to a new and emerging disease. These decisions and the ideology inherent in them were intertwined with beliefs about sexuality and sexual health. The challenge continues today as ideologic and political entities criticize the National Institutes of Health for research funding decisions, not on the basis of scientific merit, but because these groups and persons find research about commercial sex workers, truck drivers, and sexually transmitted diseases to be inappropriate as public health research topics (12). In this example, ideology pushes political action to question science and compromise public health.

In each of the cases so far described, both politics and ideology have come into play, and when ideology clouds scientific and public health judgment, decisions go awry and politics become dangerous. Having an ideology or even shouting it from rooftops is perfectly appropriate. One of the fundamental freedoms in our country is the right to believe what we want and express it. But when a person's beliefs bring about public policies that hurt people, they should be held accountable. Condoms and abstinence are well-established, effective means of birth control and STD prevention (13). Both have flaws in practical application. Both can be tools in our pursuit of improved health. The denigration of either practice suggests a preference for ideology over science.

Scientists and public health professionals often offer opinions on policy and political issues, and politicians offer theirs on public health policies, sometimes with the support of evidence. This interaction is appropriate and healthy, and valuable insights can be acquired by these cross-discussions. Nevertheless the interaction provides an opportunity for inappropriate and self-serving commentary, for public grandstanding, and for promoting public anxiety for partisan political purposes. Public health professionals should work with politicians to resist ideologic influence, to demand good science, and to make wise decisions and policies.

Conclusion

For scientists focused exclusively on winning at "NIH

bingo," accumulating R01s, KO1s, K15s, RO3s, R13s, and R21s, the interplay between science and politics may be irrelevant. However, most public health scientists and practitioners want to see their efforts improve the public's health. At the same time, scientists require an environment that permits them to work as efficiently and objectively as possible.

The issue can be succinctly addressed with a simple diagram (Figure). On the left is science, essential to inform the practice of public health. In the middle is public health, where science is interpreted and appropriate responses are developed. And on the right is political will and policies necessary to carry out the public health impetus. The tendency is to struggle against the intrusion of politics when it is counter to our own opinion, ignores or misinterprets the science, or is driven by ideology beyond politics as usual. We are right to raise our voices against the intrusion of politics into public health in the second and third circumstances, but should take care in the first one.

The diagram has a clear direction of flow. Science informs public health, which leads to political change. This approach is appropriate and effective to improve health, but the process should only flow in one direction. Reversing directions in public health decision-making is just as hazardous as it is in sewage lines. Even more insidious can be the intrusion of ideology into the process, attempting to reverse the current of the science, public health, politics stream. We have seen cases where ideology or political considerations determine a desirable policy and then seek scientific justification for it, often employing faulty science. When this happens, ideology can diminish the field, discredit the discipline and its practitioners, and undermine what scientists do.

How should infectious disease scientists handle political and ideologic pressures in their own work? One way to handle these pressures is to be connected to the rest of the public health community. Every area of public health faces the same issues: a similar commentary would apply to chronic disease or environmental health. Science and politics are intertwined in myriad ways, and ideologic influences are encountered everywhere. Tremendous concern exists in the United States about infectious diseases. Infectious diseases research no doubt gained the spotlight, and accompanying resources, after the events of September 11, 2001, and the anthrax attacks later that year. But political winds change quickly, and this focus could easily shift.

The infectious disease community needs to see their role within the larger public health context and work actively to forge alliances and collaborations between their work and the work of others. The diagram can continue to flow in the right direction, science to public health to policy, but maintaining this direction requires work, which can be accomplished by recognizing interconnectedness and using the political system to improve public health through good science. Several concrete ways to accomplish the goal exist: 1) Be an advocate for infectious disease control, not just emerging infectious diseases or bioterrorism. 2) Be an advocate for public health, not just infectious diseases. 3) Be an advocate for wise public policy based on science in the context of broader societal considerations. 4) Respect the value of the interplay of science, public health, and politics, but recognize any reversal of flow and resist it when it occurs. We all need to be strong advocates for good science, good public health, and good policies and the positive value that politics can provide for all three of these.

Figure. Proper (A) and improper (B) pathways of developing public health policy.

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Dr. McPheeters is a healthcare epidemiologist whose work focuses on translation and use of research in policy and practice, particularly in the areas of women's health and pregnancy care.

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Smallpox Models as Policy Tools[1]

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Mathematical models can help prepare for and respond to bioterrorism attacks, provided that their strengths and weaknesses are clearly understood. A series of initiatives within the Department of Health and Human Services brought modelers together with biologists and epidemiologists who specialize in smallpox and experts in bioterrorism response and health policy and has led to the parallel development of models with different technical approaches but standardized scenarios, parameter ranges, and outcome measures. Cross-disciplinary interactions throughout the process supported the development of models focused on systematically comparing alternate intervention strategies, determining the most important issues in decision-making, and identifying gaps in current knowledge.

The man who demonstrated that malaria is transmitted by mosquitoes, Sir Ronald Ross, developed the first mathematical model of malaria transmission in 1911. In presenting his model, Ross made the crucial point that "the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue" (1). In short, mathematical modeling is no more and no less than a tool to support clear thinking.

In the United States, mathematical models are familiar, everyday tools in engineering, business, and military applications and in most sciences. They represent hypotheses about underlying mechanisms that generate observed phenomena or the options for action and potential consequences. However, those models are rare in the biomedical-research and public health communities.

The events of September 11, 2001, emphasized that the United States should use every tool available to help prepare for, and respond to, bioterrorism. With that understanding in mind, a series of National Institutes of Health (NIH) consultations was organized to address the potential of mathematical models to help with bioterrorism preparedness and response.

The first of those, in December 2001, brought together a small group of modelers and a small group of health-policy experts. The basic idea of this meeting was to see if a productive dialogue would emerge, and one did, despite the language and culture barriers. This dialogue led to a much better understanding of what modeling could and could not do to help.

The overall conclusion of the meeting was that models can be of great value, provided that their strengths and weaknesses are clearly understood. Modelers and nonmodelers should develop realistic expectations. For instance, models will not provide accurate numerical predictions of outcomes in this context; models can be used to forecast only in fairly gross terms. The key is to look not for absolute numbers but for differences in outcomes between different strategies and between different models. The consensus from that first consultation was that models can provide a means to systematically compare alternative intervention strategies, determine the most important issues in decision-making, and identify critical gaps in current knowledge.

Those three points are not as simple and straightforward as they may seem. For instance, if modeling is going to help identify and focus on the decisions likely to have the largest effects on outcomes, the models must address actual decisions to be made in actual bioterrorism events. That first consultation highlighted the need for active engagement and creative tension between modelers and policy experts. Modelers may focus on areas that interest them but seem tangential to decision-makers. On the other hand, if only policy experts are engaged, they may concentrate on information that fits their opinions and interests. The modeling most likely to help with bioterrorism preparedness and response will emerge from scientific, operational, and policy professionals who listen to and engage each other, with real respect and candor, on a continuing basis.

A corollary conclusion from that first consultation was that modeling can provide a comprehensive, explicit

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[1]Based on a presentation at the International Conference on Emerging Infectious Diseases, March 3, 2004, Atlanta, Georgia, USA.

examination of the assumptions and logic that enter into a decision, in a way that purely verbal reasoning and debate cannot. In that sense, even if the results of a model were discarded, the modeling process alone, properly conducted, would more than return the investment.

Another way of looking at this same set of issues is the observation that many people, modelers and nonmodelers alike, seem to believe that one "right" model exists. In this context, at least, that is not likely to be the case. However, a great deal can be learned from examining circumstances in which several models disagree, whether or not they agree on some overall, qualitative result.

For example, the Figure shows output from two hypothetical models. The horizontal axis gives the fraction of a population covered by some intervention, e.g., a vaccine, and the vertical axis shows the resulting percentage reduction in death rate. At 0% coverage, the number of deaths does not change. Approaching 100% coverage, deaths are reduced nearly 100%. Both models agree that fewer deaths occur when more people are covered, but obvious differences also exist between the model results. According to model A, slightly less than 30% coverage would reduce deaths by half; according to model B, almost 70% coverage is needed to reduce deaths by the same amount.

Because these sorts of models embody hypotheses about underlying mechanisms, the differences may have to do with varying ideas about how a particular vaccine works in particular subpopulations, at particular sites, with different methods of introduction, or whether the vaccine acts synergistically with some other intervention. Many possibilities and uncertainties exist, but each of those ideas is in the models, explicitly. One should be able to clearly see what the different assumptions are, why the modelers put them there, and what data support them.

The results to rely on, of course, are those on which a number of different models agree in general terms, not precise, detailed predictions. But if models disagree, if one assumes that they were created by competent, honest modelers, the information that must be used to make the decision comes under more scrutiny. What are the assumptions? What are the most critical gaps in the data? Why is there disagreement? Reasonable differences in assumptions that give rise to a critical difference in outcomes point to high priorities for research.

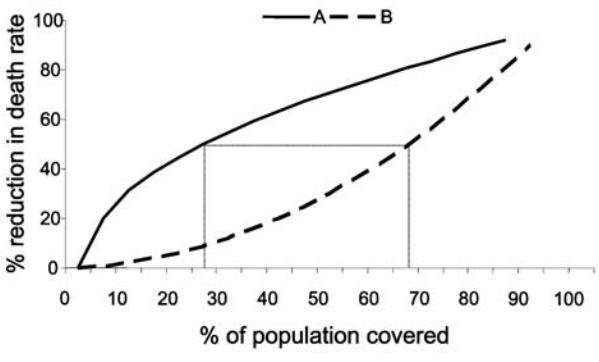

Figure. Output from two hypothetical models.

One of the recommendations from the first consultation was that a "proof of principle" project be undertaken for a specific set of issues. That recommendation was the basis of the second consultation, in April 2002, which focused specifically on smallpox modeling. The basic idea was to get a group of smallpox modelers in the same room to talk with smallpox biology and epidemiology experts and with bioterrorism-response and health-policy experts. A number of questions arose, but three stand out as examples of ways in which modeling can help to clarify assumptions.

The first of those questions was, "When does a person infected with smallpox become infectious? Is he or she still mobile, or already severely ill?" Joel Breman and D.A. Henderson had just published a review article (2), which stated, "Patients are most infectious from the onset of the enanthema through the first 7 to 10 days of rash." That is, the period of peak infectivity starts 1 day before the rash appears. Modelers interpreted that statement, and others in the literature, in a variety of ways, with slight differences in some cases and major differences in others. Differences in interpretation contributed to some of the more striking differences in model outcomes, which flagged the question as a critical one.

What is known about the infectivity of smallpox should be understood and represented in the most precise, accurate, and useful way possible. Modeling forces specific questions that help that process. If infected persons are less infectious before the onset of enanthema, how long before and how much less? Do onset and intensity of infectivity vary? By how much? How can infectivity or exposure be interpreted in terms of duration and distance of contact? The process of modeling forces an examination of the sensitivity of the results to specific answers.

The second question was, "What, in concrete, operational terms, is meant by 'ring' vaccination?" Some participants based their understanding primarily on their own experience, some on reports in the literature, and some on the Centers for Disease Control and Prevention (CDC) interim response policy of that time. Discussions of how the models had translated this first-line response strategy, now usually known as "surveillance and containment," highlighted several discrepancies and ambiguities. Similar questions arose about the meanings of "isolation" and "quarantine."

Constructing mathematical models helps make premises explicit and quantifiable, to explain what is intended by concepts such as infectivity or ring vaccination. Models are tools, but mathematical models, more than purely ver-

bal models, facilitate comprehensiveness and precision in describing assumptions and their implications.

The third question was, "How can models best represent the process by which an infectious agent may be transmitted?" The classic method of modeling considers a population to be divided into distinct subpopulations: susceptible, infected, infectious, and removed (i.e., dead or recovered and immune). Members of the population mix freely with each other, and disease spreads through contact between persons in the susceptible and infectious compartments. These models typically take the form of differential equations.

Computers have made possible a different approach to infectious disease modeling that allows modeling of interactions between distinct persons, some of whom may have many contacts during a given time period, while others have only a few. Again, differences in outcomes can arise from differences in assumptions, in this case, assumptions about social structures and mixing processes. And again, hazards of oversimplicity and overcomplexity can be remarkably subtle. For critical applications, the sensible move is to examine the sensitivity of results to specific methods by comparing different intervention strategies not only within each modeling framework but across different modeling frameworks.

Following the second consultation, the Secretary's Advisory Council on Public Health Preparedness, in the Department of Health and Human Services, formed a working group on smallpox modeling with a similar mix of people. The group was charged with developing models of smallpox spread and the potential effects of several types of interventions, in several attack scenarios, to help analyze a range of options. Specific tasks were for the working group as a whole to standardize scenarios, parameter ranges, and outcome measures. Then, modelers with different approaches (deterministic differential-equation, stochastic simulation, and individual-based simulation) were charged with developing draft models to be reviewed by the entire group, revised by the modelers, reviewed again, revised again, and so forth.

Each group of modelers is now nearly ready to submit a paper describing its model and results for peer review and publication; these articles will be accompanied by a detailed description of the common scenarios, assumptions, and parameter ranges. The aim here is to briefly outline the process the entire group went through and some of the factors considered in the models. This process has been unique in U.S. public health experience.

Achieving consensus on the scenarios and outcome measures was not difficult, at least not in comparison to the challenge of reviewing data and expert judgments and agreeing on parameter ranges and other assumptions. For all biology-epidemiology parameters, for example, ranges were expected to reflect what is known about the natural spread of smallpox, but existing information comes from efforts to treat, impede, and ultimately eradicate smallpox; the data were not collected to guide modelers, researchers, and policymakers. Thus, like most models, the models developed by the working group encompass a mixture of facts and hypotheses about mechanisms driving the dynamics at almost every level. As a result, as with most models, sensitivity analyses, which show the extent to which changes in parameters change results, make the caveats explicit and precise and also show which unknowns are most important to outcomes and most critical for research.

For example, the working group had to decide on probability distributions for the timing and intensity of key events such as incubation period, onset of fever and rash, onset and degrees of infectivity, and the like. While these discussions were often framed in biologic and clinical terms, in operational terms, the objective was to assess probabilities of case recognition, and in epidemiologic terms, the objective was to determine probabilities of transmission with various sorts of contact, to define "contact," and when possible, to calibrate everything to agreed-upon data in an agreed-upon way.

The group learned to appreciate three major disease subtypes. Since ordinary, hemorrhagic, and modified-spectrum smallpox cases differ with respect to manifestation, death rate, and transmission rate, the distribution of these subtypes in a population could affect disease spread. Accordingly, the group had to pursue related issues, such as the likely prevalence and strength of immunity in people who had been vaccinated long ago. The group also had to agree on probabilities that at any given point a person with smallpox would go to work or school, go to the hospital, or stay home. The question of who continues to circulate is influenced by manifestation and many other factors, and circulation affects not only who is likely to become infected but also who becomes a contact to be traced.

The group developed scenarios for attacks of three different sizes in terms of the number initially infected and size of the community, the site of origin, and characteristics of first cases. Age and household characteristics in the model populations reflect 2000 census data, with communities structured to incorporate homes, neighborhoods, schools, workplaces, and hospitals. Hospital characteristics reflect available U.S. data in terms of service area and population, number of beds, staff with patient contact, and so forth. The group made assumptions about the behavior of healthcare workers, isolation of patients, effectiveness of preexposure vaccine, vaccine efficacy when given at particular points postexposure, and the like.

With respect to overall intervention strategies, the group considered surveillance and containment in quanti-

tative terms, which meant thinking through parameters such as reliability of case ascertainment and efficiency of contact tracing, at various points for various types of contacts. Other possibilities included case isolation; preemptively vaccinating healthcare workers, at various levels of coverage; mass reactive vaccination, at several levels and speeds of coverage; school closings; and other measures, singly or in combination, taking into account that recognizing and confirming the first cases would be slower than with subsequent cases. Decisions such as when to expand a ring vaccination strategy to a wider community would not depend solely on epidemiologic or operational factors, but political or other factors were specifically not considered in the models.

Repeated discussions took place about the details of interventions, smallpox biology, social structures, and other factors. Typically, after a set of assumptions seemed to be in place and modelers had worked with them, related questions would emerge to be discussed, studied, and tried out. A recurring theme was the great difficulty of recognizing, untangling, and reconciling cryptic assumptions.

This sample of factors gives a good idea of the scale and scope of the working group's efforts, enough to support the claim that even if the results of the models were discarded, the process alone would justify the investment. What seem to be fairly close to final results are now emerging for the first two scenarios, and the three models seem to agree in qualitative terms with respect to intervention strategies: essentially, a prompt, thorough surveillance and containment response should be effective. Even that preliminary agreement comes with caveats, however, and exists in general terms, not necessarily in detailed predictions.

The published models should include a great deal of information, enough to allow replication with virtually any desired change in premises, parameter ranges, and scenarios. One aim of publication is to describe the structure, data, assumptions, hypotheses, and logic involved in a clear and comprehensive manner, so that each aspect can be tested, and alternate choices evaluated, by others with experience in the field. This transparency helps guard against the "garbage in, gospel out" phenomenon that plagues some modeling, policymaking, and laboratory and field studies. Peer review is beneficial, but no good substitute exists for active, ongoing involvement of multiple modelers and other experts in the process, even for less critical applications.

Participants in the December 2001 consultation recommended that "analytic modeling become an explicit element in strategic plans for biodefense preparation and response." If that is to happen, the United States needs to develop and sustain appropriate modeling expertise and access. The Working Group on Smallpox Modeling marks a small but important step in that direction. Modeling seems most likely to be of help in strategic planning and preparation (3), but the foot-and-mouth disease outbreak in the United Kingdom in 2001 suggests that real-time modeling could also be useful in an infectious disease emergency (4).

Fourier is said to have remarked, 200 years ago, that "nature is extremely indifferent towards the difficulties imposed on mathematicians" (5). But enormous sums are invested in modeling weather and economies, although the models are often wrong, and too many variables are involved to consistently obtain accurate predictions. Those investments are made because stakes are high: verbal analysis alone cannot provide solutions, and "perfect" models will never appear by magic. The same principle holds true with developing models as policy tools.

Acknowledgments

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I thank the members of the Secretary's Advisory Council on Public Health Preparedness, the Working Group on Smallpox Modeling, and participants who attended the Fogarty International Center/National Institutes of Health consultations and workshops for their many contributions.

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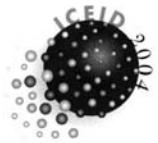

Conference Session Summaries[1]

Healthcare Settings as Amplifiers of Infectious Disease[2]

Global outbreaks of severe acute respiratory distress syndrome (SARS) in 2003 demonstrated the potential of healthcare facilities to serve as amplifiers of a new communicable disease. However, healthcare settings can also be amplifiers of multidrug-resistant bacteria and bloodborne viruses.

In the public health and healthcare delivery systems, amplifying forces include weaknesses in communication, coordination, early detection and control of emerging diseases, and oversight of healthcare services. Among healthcare personnel, weaknesses include gaps in infection control knowledge and practice.

SARS was spread globally by relatively few people and amplified by super-spreading events that occurred primarily in healthcare settings. Healthcare personnel were disproportionately affected, accounting for up to 57% of cases in some countries. The combination of increasing infectivity in the later stages of SARS, performance of the aerosol-generating procedures (bronchoscopy, intubation), and clustering of SARS patients further enhanced transmission of the SARS-associated coronavirus.

Systems for early detection and isolation of persons with suspected SARS and public quarantine effectively reduced transmission. Conversely, absence of control measures at initial points of patient encounter, particularly in hospital emergency departments, rendered hospitals particularly vulnerable to SARS transmission.

Unsafe injection and blood donation practices have contributed to the global spread of bloodborne viral diseases. Worldwide, unsafe injections alone are estimated to cause 21,000 cases of hepatitis B, 2,000 cases of hepatitis C, and 260 cases of HIV each year. Countries with limited resources are at a disproportionate risk for adverse injection-related outcomes. While lack of sterile supplies is important, unnecessary injections and poor understanding of infection control principles and practices also contribute to the spread of bloodborne viruses. These last two factors are not unique to the developing world. Four recent outbreaks of hepatitis B and C viruses in patients in ambulatory care facilities in the United States are a reminder that unsafe injections can occur in any healthcare setting. In these outbreaks, a lack of administrative oversight and poor understanding of infection control practices contributed to the contamination of multidose vials or the reuse of injection equipment and transmission of hepatitis B or hepatitis C virus to numerous patients.

In contrast to SARS and bloodborne viruses, the rise and amplification of multidrug-resistant organisms in healthcare settings have been gradual and subtle. These organisms limit treatment options, increase transmission risks for vulnerable patient populations, increase illness and death, prolong the hospital stay, and add to healthcare costs. The rise of these organisms has been most dramatic in U.S. intensive care units, where 50% of *Staphylococcus aureus* isolates are resistant to methicillin (MRSA) and 25% of enterococcal isolates are resistant to vancomycin. Cases of vancomycin-intermediate *S. aureus* and three recent cases of vancomycin-resistant *S. aureus*, both in outpatient settings, attest to the potential for amplification of these organisms in healthcare settings. Gram-negative organisms resistant to extended-spectrum β-lactamases present similar concerns and have been associated with numerous outbreaks in healthcare facilities.

The problem of multidrug-resistant organisms is multifaceted. While colonized and infected patients constitute the major reservoir for dissemination of these organisms, inappropriate use or overuse of antimicrobial agents contributes to acquiring and expressing resistance genes. Healthcare settings become breeding grounds of additional resistance and distribution centers for amplification of multidrug-resistant organisms to other healthcare settings and the community.

The notion that our healthcare settings contribute to the amplification of infectious disease contradicts our expectations. Usually, healthcare systems work well, and quality healthcare is delivered safely and efficiently. Nonetheless,

[1]Authors are the session moderators; first author for each session is the rapporteur. Actual presenters of sessions are listed in footnotes. More session summaries are available at http://www.cdc.gov/ncidod/EID/vol10 no11/iceid.htm.

[2]Presenters: Mark Loeb, McMaster University; Yvan Hutin, World Health Organization; and Larry Strausbaugh, Portland Veterans Administration Medical Center.

there are gaps in infrastructure, knowledge, and practice that can open the door to disease outbreaks.

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Transformation of the Developing World: Socioeconomic Matrix[1]

Economic disparity affects the health of persons around the world, and various societal, environmental, and economic factors influence the emergence of infectious diseases. Similarly, emerging infectious diseases have a social and economic impact, including diminished economic productivity, increased expenditures on public heath, deferred external investment and development, and reduced travel and retail sales.

The thriving consumer demand for exotic and rare animals as "tonic" food in China, especially in the southern regions, raises concern for the risk for animal-human cross-infections through contact with live and recently slaughtered animals. The increased demand for civet cat, suspected as the source of severe acute respiratory syndrome, is one such example. The demand for tonic food has risen with improving economic conditions in post-1978 China and is a form of conspicuous consumption that expresses economic and social distinction and prestige. A Chinese medical paradigm based on "humors" inherent in the concept of tonic food, combined with the well-understood cultural symbolism of distinction and prestige associated with conspicuous consumption, has lent weight to the demand for rare and exotic animals perceived to be "pure," "safe," and "virile." Since this rising demand is not likely to be suppressible, regulated production of these animals is needed to make them safe.

Additional contemporary issues in China include the effect of migration and urbanization on the spread of sexually transmitted diseases. The forces driving this effect can be divided into three overlapping categories: the dismantling of the organizational and spatial structures that helped keep order in China's cities during the Maoist era (from 1949 to 1978); a dramatic increase in the overall fluidity of urban societies in China (accompanied by the erosion of traditional moral and behavioral boundaries); and a new set of cultural values that has encouraged more urban Chinese to think of themselves as actors with individual agency. These overlapping forces, which are geographic, socioeconomic, and cultural, are interwoven with and thoroughly implicated in the emergence of new behavior and lifestyles that have put a growing number of Chinese at risk for infectious diseases.

More broadly, climate can also affect public health and emerging infectious diseases. Factors affecting emergence can also be examined in an eco-epidemiologic framework that can often drive epidemics. Examples include the effects of rains and flooding on vector-borne and diarrheal diseases and the effect of heat and fires on respiratory infections.

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Emerging Issues for the Public Health Laboratory[2]

U.S. public health laboratories face challenges from within and outside the system, including emergence of new pathogens, introduction of new testing methods, new security requirements, shortages of well-qualified personnel, and collaboration with new partners.

The public health system depends on hospital and commercial laboratories as major sources of reliable epidemiologic information. Thus, the current crisis in these laboratories is of great concern. The pressures come from the need to address emerging infectious diseases, detect antimicrobial resistance, and recognize potential agents of bioterrorism while updating procedures, practices, and facilities to meet new biosafety, biosecurity, confidentiality,

[1]Presenters: Christopher Smith, University of New York; Gerry Keusch, National Institutes of Health; Paul Epstein, Harvard University Medical School; and Josephine Smart, University of Calgary.

[2]Presenters: Roberta Carey, Centers for Disease Control and Prevention; Reynolds Salerno, Sandia National Laboratories; Bruce Budowle, Federal Bureau of Investigation; and Nancy Warren, Pennsylvania Department of Health.

and other regulations. Laboratories face a rising demand for services from an aging population at increasing risk for infectious diseases.

Clinical laboratories are receiving diminished revenues and facing increased productivity demands that result from downsizing, consolidation, and mergers. There is a shortage of qualified personnel, resulting from loss of senior staff because of retirement and difficulties in recruiting and retaining younger microbiologists. A solution to this crisis will require higher starting salaries, better tuition reimbursement, increased provision of distance learning for current staff, and increased test automation.

Bioscience laboratories are potential sources of threatening pathogens and toxins. Control of these materials is essential, but how this is achieved must be carefully considered and implemented. Potential threat agents can often be acquired from nonbioscience sources. Moreover, the nature of these materials makes their diversion difficult to prevent, and because many biological materials and technologies have dual uses, illegitimate activities can be very difficult to detect. Although many security experts believe that the most credible threat comes from persons with legitimate access to bioscience facilities, security at such facilities has largely been focused on protection against outside adversaries. Such facilities cannot be protected unless their staff understand and accept the need for security measures.

To adequately protect collections of virulent biologic agents, those responsible for the design of biosecurity systems must understand biologic materials and research and have the active involvement of laboratory scientists. Since risk will always exist and every asset cannot be protected against every threat, distinguishing between acceptable and unacceptable risks is imperative. Facilities should conduct an agent-based, security-risk assessment to ensure that protection of their assets is proportional to the risk for theft or sabotage of those assets.

The list of potential human health, animal, and agricultural threat agents is extensive. Areas at risk include not only public health and well-being, but economic well-being, public trust, consumer confidence, and the national infrastructure.

Forensic science involves applying scientific procedures to the investigation of both criminal and civil legal matters. The principal questions that microbial forensics sets out to answer are the following: What is the agent? Was the event intentional? Was the pathogen engineered? Where did the pathogen come from? and Who committed the crime? The manner in which forensic evidence is generated is critical if it is to be admissible in court. To assist law enforcement, the Scientific Working Group for Microbial Genetics and Forensics has been established. This group has identified research needs for methods to identify and type threat agents. It has established quality management guidelines for laboratories, with the goal of promoting development of forensic methods that are rigorous and scientifically valid.

Recent reports from the Institute of Medicine (1) and others recognize that the public health laboratory system has many components. The challenge presented by emerging and reemerging infectious diseases, whether these be old microbes with new scenarios (e.g., *Bacillus anthracis*), new microbes (e.g., severe acute respiratory syndrome), or old microbes with new resistance patterns (e.g., multidrug-resistant *Mycobacterium tuberculosis*), requires greater coordination between public health, clinical, and commercial microbiology laboratories. Each segment produces unique, yet overlapping, data essential to the nation's health. Essential to good coordination is communication, which can be enhanced by joint participation in meetings, collaborative studies, training opportunities, cross-cutting committees, and service on regional or national advisory boards.

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Mathematical Modeling and Public Policy: Responding to Health Crises[1]

Mathematical models have long been used to study complex biologic processes, such as the spread of infectious diseases through populations, but health policymakers have only recently begun using models to design optimal strategies for controlling outbreaks or to evaluate and possibly improve programs for preventing them. In this session, three examples of such models were examined.

[1]Presenters: Marc Bonten, Utrecht University Medical Center; Mark Woolhouse, University of Edinburgh; and Ellis McKenzie, National Institutes of Health.

Antibiotic Resistance in Hospital Settings

Patient dependency characterizes the epidemiology of disease transmission within multiple small wards with rapid patient turnover. Other variables affecting the epidemiology of resistance are the use of antimicrobial agents, introduction of colonized patients, and efficacy of infection-control measures. A Markov chain model originally made for vector-borne diseases was used to elucidate the relative importance of different routes within intensive care units.

Managing Foot-and-Mouth Disease Epidemics

State-of-the-art modeling approaches were used in Britain during the outbreak of 2001 to address such questions as: Were planned control policies sufficient to bring the epidemic under control? What was the optimal intensity of preemptive culling? Would a logistically feasible vaccination program be a more effective control option? This "real-time" use of models, although of help in devising an effective control strategy, also proved controversial.

Developing Smallpox Models as Policy Tools

Although models of infectious diseases have influenced public policy, that process and its results could be improved by regular, direct contact and communication between modelers, policy advisors, and other infectious-disease experts. At the U.S. Department of Health and Human Services, the Secretary's Council on Public Health Preparedness is sponsoring initiatives using various modeling approaches to assess biodefense strategies.

Common themes in this session were: 1) involving substantive experts, thereby ensuring that conceptual frameworks underlying the mathematics are faithful to current understanding of complex natural phenomena, 2) including all possible interventions, which could then be evaluated alone or in various combinations, and 3) identifying inadequacies in available information, for augmentation through further research.

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Public Health Workforce Development[1]

Until the early 1990s, most of Uganda's public health workforce obtained master's degrees from abroad. The responsibility for health training institutions has been shifting between the Ministry of Health and the Ministry of Education, although it is currently under the Ministry of Health, also the main employer of public health workers. The Ugandan Public Health School Without Walls is an innovative and sustainable model of worker development, conceived in 1994 in partnership with Makerere University, which houses the program; the Ministry of Health; and the development partners, notably, the Rockefeller Foundation, the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO). Up to 145 professionals from medical, biologic, and social sciences have been trained in a 10-year period. The curriculum is flexible and is constantly reviewed and adapted to the local situation. The program is 75% field-based, during which trainees are placed in 15 district training sites under professional working conditions and they also rotate through various Ministry of Health programs, where they get hands-on training. The program emphasizes operational research, dissemination of findings to policymakers, and evidence-based management decisions, features that have translated into marked improvements in the quality of the delivery of health systems in the country. Students participate in both national and international outbreak investigations. Challenges include increasing the numbers of students to match the high demand and increasing the number of learning facilities. Ensuring effective mentorship, appropriate recruitment, career paths for graduates, and sustainability of the program with reduced donor funding are also problems.

Other examples of international public health worker development initiated by WHO and its Communicable Disease Surveillance Response unit for development of training materials in partnership with CDC are the Lyon 2-year training program for laboratory specialists and epidemiologists, Global Outbreak Alert and Response Network, and various internships.

The Council of State and Territorial Epidemiologists (CSTE) conducted an Epidemiology Capacity Assessment survey of all states and territories. As of November 2001, a total of 1,366 persons were employed as epidemiologists in the 44 responding state and territorial health departments; almost half (47.7%) of these epidemiologists were working in infectious disease. The survey found that 42%

[1]Presenters: Margaret Lamunu, World Health Organization; Matt Boulton, Michigan Department of Community Health; and Lou Turner, North Carolina Public Health Laboratory.

of all epidemiologists working in state and territorial health department have no formal academic training in that discipline. States reported that approximately 48% of epidemiologists work in infectious diseases (a figure that is close to optimal), but that the rest of the public health disciplines, such as chronic disease, maternal child health, occupational health, oral health, bioterrorism/emergency preparedness, injury, and environmental health, are far below optimal capacity; further, >60% of states epidemiologic funding support comes from federal sources. Most states reported having an insufficient number of epidemiology staff and resources to carry out essential public health services.

In response to the training needs identified by this assessment, CSTE, CDC, and Association of Schools of Public Health developed a 2-year applied epidemiology training fellowship that places trainees in state health departments. CSTE hosted the first national epidemiology workforce summit in January 2004 to identify strategies for building epidemiologic capacity in the U.S. public health system.

Infectious disease testing is one of the core capacities of public health laboratories. Such laboratories play a key role in supporting outbreak investigation and surveillance activities. Public health laboratory staff must meet unique requirements and posses technical skills that require a long learning curve. Staff also need to have the knowledge of public health principals and relevance of their work to public health activities. Special recruitment and retention issues are challenging the public health laboratory workforce, including increasing vacancy rates and an increasing demand for skilled workers in light of the Select Agent Rule. At the same time, technology is changing rapidly, with new tests emerging almost daily. Solutions offered were salary parity with the private sector, innovative training, creation of interest in laboratory sciences, and continuing education. The National Laboratory Training Network has helped by offering courses, and Emerging Infectious Diseases fellowships are also attracting new workers. In 2000, Association of Public Health Laboratories survey of state laboratory directors led to the "Green Book," which forecasts impending vacancies up to 40% in certain public health laboratory areas. This finding led to the development of the Center for Public Health Laboratory Leadership, which offers corrective courses and ventures.

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Methicillin-Resistant *Staphylococcus aureus*[1]

Methicillin-resistant *Staphylococcus aureus* (MRSA) is first and foremost a pathogen of healthcare settings. It is the most common pathogen associated with nosocomial infections in the United States, particularly nosocomial pneumonia and surgical site infections. It is also a frequent cause of bloodstream and skin and soft tissue infections. The percentage of *S. aureus* isolates resistant to oxacillin/methicillin in U.S. intensive care units increased from 30% to 40% in the mid-1990s to 57% in 2002.

Data from a recent Duke Infection Control Outreach Network survey indicate that of patients with healthcare-associated MRSA infections, 39% were from nursing homes, 37% had been hospitalized in the previous 90 days, 10% had received home health care, and 10% received dialysis. Data suggest that MRSA bacteremia is associated with an increased likelihood of death, longer hospital stays, and increased cost of hospitalization, when compared with bacteremia levels caused by methicillin-susceptible strains. Increasing resistance to vancomycin among MRSA also complicates therapy, which is already difficult because of multidrug resistance among healthcare-associated MRSA. Because spread of MRSA in healthcare settings is often clonal, hand hygiene and barrier precautions are often effective in interrupting spread. Targeted surveillance for MRSA is also a useful aid for infection control. Data from the Duke network indicate that the spread of MRSA can be curtailed in healthcare settings, given vigilance and adequate funding of infection control activities.

MRSA is now spreading in community settings. Reports from the early 1980s indicate that patients in the community without established risk factors for MRSA (i.e., recent hospitalization, residence in a long-term care facility, or dialysis) sought medical care with MRSA infections. In the late 1990s, four children in Minnesota and North Dakota died from community-associated MRSA

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infections. The isolates were susceptible to most non-β-lactam drugs, had pulsed-field gel electrophoresis (PFGE) profiles that differed from typical healthcare-associated MRSA, and contained the Panton-Valentine leukocidin toxin. Prospective surveillance for MRSA in Minnesota at 12 sentinel hospitals (6 in metropolitan areas and 6 in rural areas) indicated that community-associated MRSA patients were significantly younger than healthcare-associated MRSA patients and more likely to have skin and soft tissue infections than respiratory or urinary tract infections. A study in Texas showed that incision and drainage of abscesses due to community-associated MRSA was more effective management than administering antimicrobial agents alone, particularly since many patients were given ineffective antimicrobial agents (i.e., β-lactam agents).

Molecular analysis of the community-associated MRSA strains showed that the methicillin resistance gene *mecA* is typically carried on a much smaller genetic element than is seen in healthcare-associated MRSA. Four distinct elements, called staphylococcal chromosome cassette mec (or SCCmec), have been described. In the United States, SCCmec type II, which is approximately 60 kb in size and also carries an erythromycin resistance determinant, predominates among healthcare-associated MRSA, while SCCmec type IV, which is only 23 kb in length and carries no other resistance determinants, is typically associated with community-associated MRSA. Three major strain typing methods, PFGE, multi-locus sequence typing (MLST), and staphylococcal protein A typing (spa typing), are used to study the spread of MRSA. MLST identified a series of five major lineages (also called clonal complexes) of MRSA globally, while spa typing and PFGE subdivide this group into approximately a dozen epidemic clones. Virulence determinates for MRSA include a series of enterotoxins, toxic shock toxin, and the Panton-Valentine leukocidin toxin.

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Battling 21st-Century Scourges with a 14th-Century Toolbox[1]

A range of quarantine approaches were used in five jurisdictions heavily affected by the outbreak of severe acute respiratory syndrome (SARS) in 2003. Implementation of modern quarantine was resource intensive, involved coordination of multiple sectors of society, frequently required new legislative actions or authorities, and was highly dependent on effective communication.

In Toronto, Ontario, Canada, quarantine ranged from home quarantine with active surveillance to enhanced passive surveillance augmented by education about prevention and a contact number to call if symptoms developed. Healthcare workers were occasionally required to adhere to "work quarantine." New legislation in Ontario authorized compulsory quarantine with active follow-up for compliance. Although 30,000 people in Toronto were recommended for quarantine, enforcement orders had to be issued in only 27 instances. A comprehensive infrastructure was developed to support those in quarantine; masks, thermometers, food, and financial assistance, as well as psychosocial support, were provided. Should SARS return to Toronto, the same measures would be used to ensure that close contacts of infected persons are isolated and actively monitored.

In Taiwan, from April 28 to July 4, 2003, travelers arriving from World Health Organization–designated SARS-affected areas were quarantined for 10 days (level B quarantine). During the SARS epidemic, 50,319 persons who were close contacts of SARS patients were placed under level A quarantine; suspected or probable SARS was diagnosed for 112 (0.22%). A total of 80,813 persons were placed under level B quarantine; 21 (0.03%) of these cases were diagnosed as suspected or probable SARS. The strategies were later modified as understanding of the infectivity of SARS increased, so that close contacts and travelers from local transmission areas were required to follow guidelines of self health management, including isolation at home only when they had a fever. Fever monitoring at international ports initially continued year-round; its ongoing utility will be further examined.

Singapore relied on effective quarantine of all persons who had unprotected close contact with symptomatic case-patients. Critical systems were implemented for quarantine

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policy and practice, legislative backing, communications, enforcement and surveillance, safeguards on public transport and hospital visits, financial support, operational costs, and compensation. As the gravity of the situation became clear, the Infectious Diseases Act was invoked to impose quarantine on exposed, potentially infectious persons. A Quarantine Board was set up to assist with decisions on a case-by-case basis. An important lesson was the value of clear communication. As part of a comprehensive financial and social support system, the government offered an allowance to self-employed persons to compensate for part of their lost income and to establishments with affected employees.

In Hong Kong, medical services were severely disrupted when 380 healthcare workers became ill with SARS. From April to June 2003, the economy lost an estimated U.S.$3 billion, gross domestic product growth fell by 3.7%, and exports slumped by 13.9%. SARS was controlled by a combination of measures, including disease surveillance, isolation of cases, heightened infection control, contact tracing, quarantine, entry and exit screening, and community engagement. Hospital isolation facilities and infection control training were strengthened by adding 1,000 extra isolation beds and a U.S. $20 million training fund. Retrospective analysis showed that SARS developed in 2.7% of household contacts in home quarantine, and approximately 90% of all case-patients had an identifiable epidemiologic link. Entry and exit screenings that use health declarations and temperature checks, which detected only two cases during the outbreak, have covered 90 million passengers, 5,000 of whom had fever. Addressing surge capacity was a key issue, in which the private medical sector and nongovernmental organizations proved pivotal in providing medical services, community education, and support for emergency operations, including quarantine both at home and at dedicated residential facilities.

Beijing, China, experienced the world's largest outbreak of SARS in spring 2003 with 2,521 reported probable cases. Quarantine played an important role in controlling the outbreak. By July 1, a total of 30,178 persons, 0.21% of the Beijing population, had been quarantined. Most close contacts were quarantined at home (60%); the rest were at designated sites, including hotels, universities, and construction worksites. In late April, fever checks were instituted at the airport, major train stations, and all 71 roads connecting Beijing to other areas; these sites used infrared thermometers to screen and axillary thermometers to confirm fever among passengers. As of June 30, 2003, of almost 14 million people screened, only 12 probable cases of SARS were identified. All healthcare workers in SARS-designated hospitals had to stay in designated hotels close to the hospitals rather than at home. After finishing their work with SARS patients, they were sent to resort areas for 2 more weeks. Top challenges for implementing quarantine included tracing contacts, maintaining movement restrictions even at home, and finding the resources to provide 10,000 people with supplies and psychological care. Nonetheless, the same quarantine measures will be implemented if SARS returns.

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Tuberculosis and Sexually Transmitted Infections

To the Editor: *Mycobacterium tuberculosis* infection is a necessary, but not sufficient, cause of tuberculosis (TB). Infection with HIV is the strongest known risk factor for disease progression to TB. In the absence of HIV infection, disease develops in 5% to 15% of infected persons. Unfortunately, the process of progression to disease is poorly understood. We hypothesize that, in addition to HIV, another sexually transmitted infection (STI) also increases such disease progression. Identification of this STI might suggest new approaches to disease control.

Several associations between the risk for TB and lifestyle factors have been identified (1). For example, unmarried persons are at higher risk than married persons. A correlation between TB and body mass index has also been shown; the risk of tuberculosis decreases as body mass index increases. Whether these risk factors reflect an increased risk for tuberculous infection or an increased risk for disease progression is not clear, however.

Risk factors for tuberculous disease progression itself have also been studied. Several medical conditions, e.g., hemophilia, kidney disease requiring hemodialysis, HIV infection, diabetes, some kinds of cancer, and silicosis, increase the risk of progression to disease (1). Another consistent finding is that age affects risk. Infants and children with immature immune systems appear to be at high risk for developing tuberculous meningitis. After the immune system matures, children appear to be rather resistant to disease progression until puberty; only 1% to 3% of infections progress to manifest disease, and pulmonary TB is rare. This resistance is largely lost after puberty, an association that seems causal. Dubos and Dubos noted "In the majority of girls, pulmonary lesions were first found in the age group of 13 to 15 years, with a striking relation to the onset of menses" (2). Evidence that sex hormones play a role in this loss of resistance is shown by a study on the effects of male castration on longevity (3). This study found that castrated, mentally handicapped patients, in the first half of the 20th century in Kansas, outlived patients who were not castrated by more than 10 years, mostly due to measurably lower TB death rates. Although this finding may reflect the direct effect of sex hormones on the immune response to tuberculous infection, we believe that it is more consistent with exposure to an as yet unidentified STI. The STI hypothesis not only explains the mechanisms behind the lifestyle risk factors discussed above, namely by confounding with sexual behavior, but also why TB has ceased to be a major cause of death in Western societies.

In the Netherlands, deaths due to TB declined consistently during the first half of the 20th century. During World War II, however, deaths due to TB almost doubled, even before living conditions deteriorated. After the war, deaths due to TB plummeted, falling almost 10-fold between 1945 and 1955, essentially before the advent of effective chemotherapy (4). Similar declines in deaths due to TB were observed in other industrialized countries during this period. No satisfactory explanation has been given for this pattern. Only a drop in TB progression rates could likely account for this decline because, as for much of Europe, the early postwar period was a time of scarcity and housing shortages, which rules out decreases in crowding and transmission as plausible explanations. This scarcity would also seem to exclude nutritional factors as a probable cause of falling disease progression rates. However, this epidemiologic history is very similar to that of STIs, e.g., syphilis (5) and may not be coincidental.

Historic data on age-specific deaths caused by TB from Massachusetts, 1880–1930 (6), show that deaths among women tended to peak at lower ages than deaths among men, which is similar to patterns of STI prevalence. This "young women, older men" pattern is found in most populations in which TB is endemic and appears to be caused by age- and sex-specific differences in risk of disease progression, because these differences are not found in TB infection prevalence (7). Such a pattern would seem more consistent with our STI hypothesis than with a direct hormonal effect on TB disease progression rates.

The association between TB and sexual behavior has rarely been studied, except within the context of HIV infection. In one study, conducted in Los Angeles, many HIV-negative TB patients reported high-risk sexual behavior (8), but in the absence of a control group, this finding provides only anecdotal support of our hypothesis. Recent evidence comes from a study on prison inmates in the United States in which inmates who reported a history of TB also reported higher sexual risk factors than those without such a history, although confounding by HIV infection cannot be entirely ruled out (9).

Which pathogen may be responsible for the other STI? The association of susceptibiblity risk with hemophilia and hemodialysis suggests that it is a filterable agent, for example, one of the many herpesviruses. Many of these are sexually transmitted, and some, e.g., Epstein-Barr virus and cytomegalovirus, have immunosuppressive properties and infect macrophages, cells that are key in the immune response to *M. tuberculosis*. Viral strategies of evading the immune system inside these cells may well

create a niche for *M. tuberculosis* (10).

Our hypothesis could be refuted or corroborated in several ways, for example, by a case-control study of HIV-negative patients infected with tuberculosis. If this study refutes our hypothesis, the idea that sex hormones play a direct role in the immune response to *M. tuberculosis* would be supported. Such findings might also provide possibilities for drug development. However, if case-control studies support our hypothesis, attempts should be made to identify the pathogen.

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Leptotrichia amnionii and the Female Reproductive Tract

To the Editor: Detection of new bacteria, human complex microflora, by using 16S rRNA gene amplification and sequencing has been reported (1). 16S rRNA gene amplification and sequencing detected pyosalpinx, caused by *Leptotrichia amnioni*, in a patient whose samples were culture-negative.

This anaerobic gram-negative bacterium has been isolated only once before (2). A 41-year-old woman from the island of Comoros who had been having lower abdominal pain for 6 days was admitted to the emergency department of Hôpital Nord in Marseille. The patient's history included type 2 diabetes mellitus treated by metformin and laparoscopy to explore infertility. On examination, the patient had a pulse rate of 90 beats per min, a blood pressure of 130/80 mm Hg, and a temperature of 38.5°C. Her abdomen was not distended, but diffused lower abdominal tenderness, especially at the right iliac fossa, was present. Blood testing showed a leukocyte count of 7.7×10^9/L, hemoglobin of 13.1g/dL, and platelet count of 213×10^9/L. The chemistry panel showed hyperglycemia (14.1 mmol/L) and elevated C-reactive protein (254 mg/L). Renal and liver function test results were all within normal limits. Serum β-human chorionic gonadotropin was negative. A computed tomographic scan of the abdomen and pelvis showed two septated adnexal masses, a 12x7x5 cm mass on the right and a 6x4x2 cm mass on the left; the patient was referred to the gynecologic surgery department. Gynecologic examination showed greenish, purulent vaginal discharge and a fluctuant mass in the pouch of Douglas. Uterine cervical motion caused pain to the patient. Transabdominal and transvaginal ultrasound scan showed a 10x7x5 cm homogeneous liquid mass in the pouch of Douglas.

The patient was taken to the operating room and prepared for surgery. The gynecologic team performed a laparotomy that showed a 5-cm, left hydrosalpinx and a 10-cm, right tuboovarian abscess adherent to the uterus, sigmoid colon, pelvic sidewall, and pouch of Douglas. The appendix and other viscera were normal. The adhesiolysis led to the rupture of the abscess and discharge of clear greenish pus, a sample of which was sent to the laboratory for culture. Antimicrobial drug treatment was started with intravenous cefazolin, gentamicin, and metronidazole. On the first postoperative day, the patient was afebrile. Oral amoxicillin plus clavulanic acid was administered for 15 days, and oral ciprofloxacin was administered for 20 days. The patient was discharged on day 7 of hospitalization and was well at the follow-up examination 1 month later.

After Gram staining, a sample of the abscess drainage was injected onto Columbia agar with 5% sheep blood (bioMerieux, Marcy l'etoile, France) under 5% CO_2 and anaerobic atmosphere. Antimicrobial susceptibility of the sample was tested by an agar diffusion method (3). A drop of

the sample was deposited on an agar plate flooded with a suspension of a antimicrobial susceptible strain of *Micrococcus luteus.* After 24 h of incubation at 37°C, presence of antimicrobial activity in the sample was evident by a visible area of growth inhibition of *M. luteus* around the sample. Procedures for DNA extraction and16S rRNA gene amplification and sequencing have been detailed (4).

Gram staining of the sample showed numerous polymorphonuclear leukocytes and gram-negative bacteria. Culture of the sample remained sterile after 20 days of incubation, and antimicrobial susceptibility was found. The 16S rRNA gene amplification and sequencing determined a 1,493 nucleotide sequence. This sequence had 99.7% nucleotide similarity with that of *L. amnionii* (GenBank accession no. AY078425), which corresponded to a difference of 4 nucleotide. The 16S rRNA gene sequence of the detected bacterium was deposited under accession no. AY489565. *L. amnionii* was previously recovered in anaerobic culture of the amniotic fluid of a woman after intrauterine fetal demise (2). It was isolated on blood and chocolate agar under anaerobic conditions and showed very small gray colonies of <1 mm. This slow-growing bacterium was lost after two subcultures, and no isolate is available for further description (2). In that case and in the case reported here, the patients had uneventful recoveries after an amoxicillin plus clavulanic acid antimicrobial regimen was given. This bacterium and our isolate are related to, but different from, *L. sanguinegens*.

Leptotrichia is a small genus closely related to *Fusobacterium* and comprises slow-growing, gram-negative, filamentous, anaerobic bacterial flora of the oral cavity and genital tract (5). Species included in the genus are *L. buccalis*, *L. trevisanii*, *L. sanguinegens*, and *L. amnionii* (2,6). All *Leptotrichia* species are extremely fastidious and cannot be grown easily on conventional microbiologic media or by conventional methods. As evidenced by sequences available in the GenBank database, most of the 16S rRNA gene sequences are from cloned DNA from complex flora but not from bacterial isolates. *Leptotrichia* species has been suspected to play a role in periodontal disease. However, *Leptotrichia* species have only been associated with serious systemic disease, usually in immunocompromised patients (7,8). Bacteremia caused by *L. sanguinegens* in pregnant women has also been reported (9). More widespread use of polymerase chain reaction amplification and sequencing of the 16S rRNA gene for identification or detection of fastidious pathogens in humans will likely provide verification of several new pathogens that are now part of normal human flora.

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Cholera in Mozambique, Variant of *Vibrio cholerae*

To the Editor: Cholera outbreaks caused by toxigenic *Vibrio cholerae* serogroup O1 frequently occur in many sub-Saharan African countries. The serogroup O1 is classified into two biotypes, classical and El Tor. The seventh and current pandemic of cholera is caused by the El Tor biotype; the classical biotype is believed to be extinct. The classical and El Tor biotypes of *V. cholerae* O1 are closely related in their O-antigen biosynthetic genes but differ in other regions of the genome. The genomic structure of the CTXΦ filamentous phage (1), in which the cholera toxin genes are contained, differs between the classical and El Tor biotypes. $CTX^{class}\Phi$ is found in classical strains, $CTX^{ET}\Phi$ is

present in El Tor and O139 strains, and CTX$^{calc}\Phi$ is found in resurgent O139 strains. The diversity of CTXΦ among biotypes is mainly due to the variations in the repeat sequence elements, particularly in the *rstR* gene region (2).

While conducting surveillance in the cholera treatment center in Beira, the second largest city in Mozambique, we examined 175 rectal swabs or stool samples from January 7 to March 8, 2004, using standard published procedures. During this period, we isolated 58 strains of *V. cholerae* O1. The isolates were transported to the Enteric Microbiology Unit of the International Center for Diarrhoeal Disease Research in Dhaka, Bangladesh (ICDDRD,B), for further phenotypic and genotypic characterization to determine serotype, biotype, and presence of important virulence genes. All 58 strains were identified as *V. cholerae* O1 of the Ogawa serotype. Forty strains selected for detailed characterization were resistant to polymyxin B, agglutinated chicken cells, yielded a positive Voges-Proskauer reaction, were positive for the El Tor hemolysin by the tube agglutination method, and were sensitive to group IV El Tor phage but resistant to the classical group V phage and were therefore classified as the El Tor biotype. The antimicrobial susceptibility of 15 of the 40 isolates examined showed that the strains were sensitive to tetracycline, ampicillin, furazolidone, erythromycin, and ciprofloxacin but resistant to trimethoprim-sulfamethoxazole, and also to the vibriostatic compound 0/129.

By using polymerase chain reaction (PCR), we established that all 40 strains carried the *ctxA* gene (constituent gene of the CTX prophage) and the *tcpA* gene (the El Tor type), a constituent gene of the vibrio pathogenicity island. We then focused on the *rstR* gene because of its diversity between the two biotypes. All of the 40 El Tor strains produced a 500-bp PCR product of the *rstR* gene of the classical type (*rstR*^{class}), despite belonging to the El Tor biotype. Nucleotide sequence analysis of the *rstR* gene of two representative Mozambique strains showed 100% homology to the classical *rstR* gene of classical reference strain O395. The amino acid sequence of the B-subunit of classical and El Tor biotypes have distinct signature sequences (3). We amplified the *ctxB* gene using specific primers and found that the deduced amino acid sequence of the CT-B subunit of the Mozambique strains varied from the El Tor CT-B subunit at positions 39 (histidine replaces tyrosine in El Tor) and 68 (threonine replaces isoleucine in El Tor), and the amino acid residues at these positions are identical to those of the classical CT-B subunit (Figure). The nucleotide sequences obtained for *ctxB* of the two Mozambique strains B33 and B65 were deposited in GenBank under accession no. AY648939 and AY6448940, respectively. Therefore, the Mozambique strains of *V. cholerae* O1 displayed typical traits of the El Tor biotype overall but carried the classical CTX prophage.

Our findings that El Tor strains of *V. cholerae* O1 from Mozambique are carrying the classical prophage shows the presence of genetic materials associated with the classical biotype in Mozambique. Further, these findings provide the first circumstantial evidence of transmission of the classical CTX prophage. The CTX prophages in El Tor strains give rise to infectious phage particles (1), but neither of the two CTX prophages integrated at two different sites of the classical genome give rise to phage particles (4). Subsequent studies have shown that, although the genes of the classical prophages encode functional forms of all of the proteins needed for production of CTXΦ, the CTX prophage does not yield virions because of the atypical arrangement of its prophage arrays (4).

Genetic hybrids between El Tor and classical biotypes of O1 *V. cholerae* were reported among sporadic isolates earlier in Bangladesh (5) and were named the Matlab variants after the place where they were first isolated. The Mozambique strains of *V. cholerae* likely evolved from an El Tor strain, which shed its CTX phage and acquired the classical prophage. Alternatively, strains like the Matlab variant may have spread to the African subcontinent. Whether introducing the CTX prophage in the El Tor genome background will increase pathogenicity, affect genomic stability, or enhance the epidemic-causing potential is uncertain. This subtle genetic change might also alter the effectiveness of current cholera vaccines which stimulate antitoxic as well as antibacterial immunity.

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                                1                                   39          55
V. cholerae Classical : MIKLKFGVFFTVLLSSAYAHGTPQNITDLCAEYHNTQIHTLNDKIFSYTESLAGK
V. cholerae Classical : .............................................L........N
V. cholerae O1 B33    : ....................................................
V. cholerae O1 B65    : ....................................................
V. cholerae El Tor    : ....................................Y...............
V. cholerae El Tor    : ....................................Y...............

                          56        68                                  104
V. cholerae Classical : REMAIITFKNGATFQVEVPGSQHIDSQKKAIERMKDTLRIAYLTEAKVE
V. cholerae Classical : ....................................................
V. cholerae O1 B33    : ....................................................
V. cholerae O1 B65    : ................G...................................
V. cholerae El Tor    : ............I.......................................
V. cholerae El Tor    : ............I.......................................
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Figure: Amino acid sequence alignment of CT-B subunit of *Vibrio cholerae* O1 classical, El Tor, and Mozambique (B33 and B65) strains. Identical amino acid residues are indicated by a period. Amino acid sequences of CtxB of *V. cholerae* classical (AAL60524.1; AAM47189.1) and El Tor (AAM74192.1; AAM77066.1) are from GenBank.

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Correction, vol. 10, no. 10

In "Scrub Typhus in the Republic of Palau, Micronesia," by A. Mark Durand et al. (p. 1840), Table 2 was incorrect. The correct version appears below and online at http://www.cdc.gov/ncidod//eid/vol10no10/04-0288.htm#table2. We regret any confusion this error may have caused.

Table 2. *Orientia tsutsugamushi* IgG and IgM antibody titers for six southwest islanders with prolonged fever and abdominal distress[a]

Patient no.	Antibody type	Acute-phase titer	Convalescent-phase titer
1	IgG	1:2,048	NA
	IgM	1:16,384	NA
2	IgG	NA	1:32,768
	IgM	NA	1:2,048
3	IgG	1:262,144	1:262,144
	IgM	1:4,096	1:1,024
4	IgG	1:65,536	1:65,536
	IgM	1:1,024	1:2,048
5	IgG	1:8,000	1:64,000
	IgM	NA	NA
6	IgG	1:4,000	1:64,000
	IgM	NA	NA

[a]Ig, immunoglobulin; NA, result not available.

Instructions for Emerging Infectious Diseases Authors

Letters

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Vaccines: Preventing Disease Protecting Health

Ciro A. de Quadros, Editor
Pan American Health Organization, World Health Organization

ISBN: 92-75-11596-6
Pages: 412, Price: U.S. $59.95

Vaccines: Preventing Disease Protecting Health does not provide the type of vaccine-specific information as Plotkin and Orenstein's Vaccines (1), nor does it provide the details on the immune system of Bloom and Lambert's The Vaccine Book (2). The book does not cover every important vaccine issue, such as ethical issues in vaccine trials and the conduct of clinical trials; most critically, it lacks an index. But these limitations are minor compared to what the book provides.

This relatively small book provides state-of-the-art information by those who are directly involved with vaccine and immunization programs. The book evolved from a meeting held November 25–27, 2002, in Washington, D.C., at which many of the world's top vaccine scientists reported on their research. As the book jacket states, the roster of authors reads like a Who's Who in vaccine research and public health immunization programs. This publication comes from the Pan American Health Organization (PAHO), the World Health Organization (WHO) Regional Office, which has been at the forefront of almost every major vaccine initiative for the past 30 years, including the eradication of polio, elimination of measles, and strategies to control rubella and neonatal tetanus. These programs have served as models emulated by other WHO regions in the world. The editor, Ciro A. de Quadros, former director of PAHO's Vaccine and Immunization Program, has a scholarly hand, as well as an eye towards what is practical and useful. This book conveys not only what has been achieved in the arena of vaccine-preventable diseases in the 30 years since the first such conference was convened by PAHO in 1970 but also what is most likely to happen during the next 30 years.

The chapters are quick and painless reading, in many cases directly from those involved in the research described. For example, Peter F. Wright, one of the leading researchers on respiratory syncytial virus (RSV) vaccines, provides this candid assessment: "The road leading to the development of a vaccine for the prevention of RSV has been so difficult and the prospects for a vaccine remain so daunting, that only the impact of the disease provides the imperative for researchers to continue in their quest." Michiaki Takahashi, one of the developers of the varicella vaccine, provides insights on breakthrough cases occurring in "15–20% of vaccine recipients." Takahashi also reports on the status of a vaccine to prevent herpes zoster in older persons. Roger Glass et al. provide a succinct update on rotavirus vaccines currently in development and human trials.

Even highly technical aspects of new vaccine development, such as DNA vaccines, are dealt with clarity in relatively brief presentations. Topics not always found in other vaccine books include those on antihookworm vaccine, mucosal vaccines, and oral vaccines derived from transgenic plants. The chapter on new polio vaccines is coauthored by Eckard Wimmer, who achieved worldwide fame by using the poliovirus' known genetic sequence to synthesize that virus from the building blocks of DNA and a broth of other chemicals.

Overall, the book includes several scenarios. "The Present" section concerns controlling diseases for which there are available vaccines; "The Cutting Edge" section concerns recently introduced vaccines. "The Future" concerns candidate vaccines on the horizon; "The Quest" section concerns challenging areas for vaccine development, which include HIV/AIDS, malaria, and dengue. Other sections include "New Concepts," "Delivery Systems," "Bioterorrism," "Regulatory and Safety Issues," as well as "Health Financing." To some degree, the book's descriptive and detailed table of contents makes up for the absence of an index. While hard to believe, this book about vaccines and vaccine programs is hard to put down because of its readability.

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Conference Summary

National Antibiotic Resistance Monitoring System for Enteric Bacteria

National Antibiotic Resistance Monitoring System (NARMS)–enteric bacteria is a collaboration by the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration, the Center for Veterinary Medicine (FDA-CVM), and the U.S. Department of Agriculture, Agricultural Research Services (USDA-ARS). NARMS was established in 1996 and monitors antimicrobial drug resistance in *Campylobacter*, *Escherichia coli* O157:H7, *Enterococcus*, non-Typhi *Salmonella*, *Salmonella* Typhi, and *Shigella*.

The 2004 meeting was held March 4–5 in Decatur, Georgia, and hosted by the Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, CDC. The meeting highlighted data from scientific studies and surveillance for antimicrobial drug resistance in the United States and abroad with enteric bacteria isolated from humans, animals, and retail foods. Approximately 180 participants from 14 countries, representing 71 organizations, attended the meeting. The organizations included international and national public health agencies, state and local health departments, public health laboratories, industry consumer groups, and academic institutions from Australia, Canada, Cameroon, China, Denmark, Europe, Italy, Japan, Philippines, Poland, Thailand, the United Kingdom, the United States, and Vietnam.

The meeting began with a World Health Organization expert's summarization of a recent workshop on nonhuman antimicrobial drug use and antimicrobial drug resistance. Scientific assessment and risk management of antimicrobial drug use in agriculture and human and veterinary medicine were examined. A plenary session on the human health consequences of antimicrobial drug resistance consisted of two presentations from the United States and two presentations from Denmark.

The results of a study conducted by CDC that found higher rates of hospitalization and death in resistant *Salmonella* infection, as compared to susceptible ones, were presented. The results of another CDC study that found higher frequencies of bloodstream infection and hospitalization with resistant *Salmonella* infections, as compared to susceptible ones, were presented. A presentation from the Statens Serum Institut in Denmark highlighted the association between flouroquinolone-resistant *Campylobacter* infections, as compared to susceptible ones, and a higher frequency of invasive illness, hospitalization, and death. A second presentation demonstrated increased death rates in resistant *S.* Typhimurium infections, as compared to susceptible ones. Other speakers highlighted emerging resistance to clinically important antimicrobial drugs, environmental studies on antimicrobial drug resistance, antimicrobial drug resistance in commensal bacteria, partner perspectives on antimicrobial drug resistance, international perspectives on antimicrobial drug resistance, and NARMS educational activities. A presentation of the "GET SMART: Know When Antibiotics Work on the Farm" campaign highlighted educational efforts to promote the appropriate use of antibiotics in veterinary medicine. The campaign currently includes an interactive Web-based program on aspects of microbiology, pharmacology, infectious disease, and public health for veterinary students and veterinarians who participate in continuing education programs. The conference also included brief summaries of three recent outbreaks of multidrug-resistant *S.* Typhimurium DT104 R-type, which has become a common strain of *Salmonella* isolated from humans and was resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines. More information about NARMS and antimicrobial resistance can be found at www.cdc.gov/NARMS.

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Remedios Varo (1908–1963). La Llamada (The Call) (1961)
Oil on Masonite (98.5 cm x 68 cm). Private collection, courtesy of Walter Gruen

Scientific Discovery and Women's Health

Polyxeni Potter

"Surrealism claims totally the work of the enchantress too soon gone," said André Breton, when he heard that Remedios Varo had died, in 1963 (1). Surrealism, which sought to express "the actual functioning of thought," was Varo's vehicle for understanding the universe, a vehicle that, like the fanciful locomotives in many of her paintings, went beyond established scientific principles. Bolstered by intuition and intellectual curiosity, the movement accessed the world of dreams, memory, and the psyche (2).

To this expansive world, Varo brought knowledge of engineering construction, painstaking attention to detail, a penchant for philosophical discourse, and fascination with alchemy and the occult (3). The result was a personal approach to surrealism, the unified vision of a fantastic world inhabited by creatures of the imagination, moving freely in and out of consciousness, proposing new solutions, offering alternative interpretations.

A native of Angles, Spain, Remedios Varo grew up in a family that nurtured academic and artistic aspirations. Her father, a hydraulics engineer, encouraged her interest in science and taught her how to draft images, a skill she used throughout her artistic career. At age 15, she enrolled in the renowned fine arts academy of San Fernando in Madrid, also attended around the same time by budding surrealist, Salvador Dalí.

At the academy, which featured such lecturers as Marie Curie, H.G. Wells, Albert Einstein, and José Ortega y Gasset, Varo became familiar with new ideas: the theories of Sigmund Freud, which broadened the boundaries of reality, the work of André Breton, which defined surrealism as a literary and artistic movement. She was exposed to the treasures of the Prado Museum and the influences of Hieronymus Bosch, Francisco Goya, El Greco, Picasso, and Braque.

Varo's rigorous academic training formed the backbone of an artistic career marked by innovation and creativity and frequently interrupted by conflict. The Spanish Civil War forced her to flee Barcelona, where she had become part of the bohemian avant-garde, for Paris, where she apprenticed among the surrealists' inner circle and exhibited her work widely. She left Europe to escape World War II, and Mexico became the adoptive home where in the last 10 years of her life she produced the bulk of her mature work.

Mexico, with its pre-Columbian cultures, primitive art, and abundant hospitality, provided Varo broad artistic freedom and an exciting context in which to practice surrealist rebellion. Yet, her first few years in exile were marked by economic hardship and emotional isolation: "We are finally installed here…suffering from the 2,400 meters altitude…dead with fatigue and having heart ailments" (3). Away from her familiar circle, she struggled to secure what Virginia Woolf once identified as the basic requirements for an artistic career: a steady income and "a room of one's own." She painted furniture, worked for Bayer Pharmaceuticals as illustrator, and during a brief visit to Venezuela, produced scientific drawings for that country's Ministry of Public Health (4).

Varo's interest in scientific discovery, reflected even in the titles of her works, extended to cosmology, evolution, astronomy, and genetics: The Phenomenon of Weightlessness, Cosmic Energy, Weaving of Space and Time, Creation of the Birds, Discovery of a Mutant Geologist, Exploration of the Sources of the Orinoco River, Vegetal Architecture. Her paintings showed empathetic understanding of the human condition and often contained elaborate mechanical devices and instruments of science meant to improve it.

"…as if she paints with her gaze rather than her hands, Remedios clears the canvas and over its transparent surface she gathers simple truths…" said Mexican poet Octavio Paz in his poem "Apparitions and Disappearances" (3). Her protagonists, who bear her heart-shaped face, almond eyes, long sharp nose, and abundant hair, move in a metaphysical world. As they straddle the line between real and unreal, they seem aware of their demands on the viewer's imagination. Witty and engaging, they levitate in narrative scenes filled with fantastic plant and animal life. Some cats are so wild they are made of ferns, some women so domesticated they have chair arms and chair legs.

The Call, on this month's cover of Emerging Infectious Diseases, is inhabited by apparitions and has the eerie stillness and depthless unreality of a dream. A flaming female figure charged by a celestial body emanates energy and lights up the scene; around her neck, a single ornament, a chemist's mortar; in her hand, a laboratory flask, a retort. The lurid presence casts a glow on the dim walls of a hallway. From these walls, like a hallucinogenic distortion, a mournful array of human forms bulge forward, feet anchored to the floor, eyes downcast, bodies lost in outlandish folds: female phantoms, pillars and structural support, trapped in a paralyzing nightmare.

Mysterious and provocative, the architectural stage is cluttered with conflicting clues. The walls are tall; the windows small and out of reach; the sky inflamed; the morbid folds props of oppression. Yet, the floor is elaborately tiled, the doorways arched, the steps well-tended. The stage is firmly cast, oppression is institutionalized.

Varo's enigmatic Call, part dream part symbolic reality, seems at once a calling and a call to action. The flaming figure wears the signs and halo of science. Bathed in the light of knowledge, she steps forward boldly to dispel the darkness. In the painter's surreal universe as well as ours, the female phantoms on the wall stand for poverty, confinement, disease. Overlooked by societies, biomedical research, and healthcare systems; battered by AIDS, malaria, and other infections; victimized by globalization; and stigmatized by the very diseases that confine and kill them (5), women slumber in the shadows. The flaming figure's flask contains the science. Her call is a wake-up call.

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EMERGING INFECTIOUS DISEASES

A Peer-Reviewed Journal Tracking and Analyzing Disease Trends
Vol. 10, No. 12, December 2004

Upcoming Issue

Look in the December issue, with a zoonosis theme, for the following topics:

Historical, Emerging, and Reemerging Links between Human and Animal Health

Wildlife as a Source of Zoonotic Infections

Potential Mammalian Reservoirs of Filovirus

Nipah Virus Reemergence, Bangladesh

Nonhuman Primate Exposure, Cameroon

West Nile Virus in North American Owls, Ontario, 2002

Crimean-Congo Hemorrhagic Fever, Mauritania

Origin of Amphibian Chytrid Fungus

Venezuelan Equine Encephalitis Virus, Southern Mexico

Differential West Nile Virulence for Crows

Human Illness from Avian Influenza H7N3, British Columbia

Complete list of articles in the December issue at http://www.cdc.gov/ncidod/eid/upcoming.htm

Upcoming Infectious Disease Activities

November 7–11, 2004
53rd Annual Meeting,
American Society of Tropical Medicine and Hygiene
Miami, FL, USA
Contact: 847-480-9592 or astmh@astmh.org

November 9–10, 2004
Antimicrobial Resistance and Emerging Infections: A Public Health Perspective
Philadelphia, PA, USA
Contact: 617-983-6285
neoffice@nltn.org
http://www.uphs.upenn.edu/epaasm/

November 12–14, 2004
Symposium, The Changing Landscape of Vaccine Development: Translating Vaccines for Emerging Diseases and Biodefense to the Marketplace
Galveston, TX, USA
Contact: 409-747-8151 or
http://www.utmb.edu/scvd

November 17–20, 2004
5th Louis Pasteur Conference on Infectious Diseases
Paris, France
clp@pasteur.fr
http://www.pasteur.fr/infosci/conf/sb/CLP5

December 3–4, 2004
Focus on Hospital Infections
Trump International Sonesta Resort
Miami, Florida, USA
Contact: 770-751-7332 or
c.chase@imedex.com
http://www.imedex.com/calendars/infectiousdisease.htm

EMERGING INFECTIOUS DISEASES
A Peer-Reviewed Journal Tracking and Analyzing Disease Trends

Editorial Policy and Call for Articles

Emerging Infectious Diseases is a peer-reviewed journal established expressly to promote the recognition of new and reemerging infectious diseases around the world and improve the understanding of factors involved in disease emergence, prevention, and elimination.

The journal is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health, as well as from specialists in economics, social sciences, and other disciplines. Manuscripts in all categories should explain the contents in public health terms. For information on manuscript categories and suitability of proposed articles see below and visit http://www.cdc.gov/eid/ncidod/ EID/instruct.htm.

Emerging Infectious Diseases is published in English. To expedite publication, we post articles online ahead of print. Partial translations of the journal are available in Japanese (print only), Chinese, French, and Spanish (http://www.cdc.gov/eid/ncidod/EID/trans.htm).

Instructions to Authors

Manuscript Preparation. For word processing, use MS Word. Begin each of the following sections on a new page and in this order: title page, keywords, abstract, text, acknowledgments, biographical sketch, references, tables, figure legends, appendixes, and figures. Each figure should be in a separate file.

Title Page. Give complete information about each author (i.e., full name, graduate degree(s), affiliation, and the name of the institution in which the work was done). Clearly identify the corresponding author and provide that author's mailing address (include phone number, fax number, and email address). Include separate word counts for abstract and text.

Keywords. Include up to 10 keywords; use terms listed in Medical Subject Headings Index Medicus.

Text. Double-space everything, including the title page, abstract, references, tables, and figure legends. Indent paragraphs; leave no extra space between paragraphs. After a period, leave only one space before beginning the next sentence. Use 12-point Times New Roman font and format with ragged right margins (left align). Italicize (rather than underline) scientific names when needed.

Biographical Sketch. Include a short biographical sketch of the first author—both authors if only two. Include affiliations and the author's primary research interests.

References. Follow Uniform Requirements (www.icmje. org/index.html). Do not use endnotes for references. Place reference numbers in parentheses, not superscripts. Number citations in order of appearance (including in text, figures, and tables). Cite personal communications, unpublished data, and manuscripts in preparation or submitted for publication in parentheses in text. Consult List of Journals Indexed in Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title. List the first six authors followed by "et al." Do not cite references in the abstract.

Tables and Figures. Create tables within MS Word's table tool. Do not format tables as columns or tabs. Send graphics in native, high-resolution (200 dpi minimum) .TIF (Tagged Image File), or .EPS (Encapsulated Postscript) format. Graphics should be in a separate electronic file from the text file. For graphic files, use Arial font. Convert Macintosh files into the suggested PC format. Figures, symbols, letters, and numbers should be large enough to remain legible when reduced. Place figure keys within the figure. For more information see EID Style Guide (http://www.cdc.gov/ncidod/ EID/style_guide.htm).

Manuscript Submission. Include a cover letter indicating the proposed category of the article (e.g., Research, Dispatch) and verifying that the final manuscript has been seen and approved by all authors. Complete provide authors Checklist. To submit a manuscript, access Manuscript Central from the Emerging Infectious Diseases web page (www.cdc.gov/eid).

Types of Articles

Perspectives. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch of first author. Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases and related issues. Perspectives may also address factors known to influence the emergence of diseases, including microbial adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Synopses. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch of first author—both authors if only two. This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Research Studies. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary, and a brief biographical sketch of first author—both authors if only two. Report laboratory and epidemiologic results within a public health perspective. Explain the value of the research in public health terms and place the findings in a larger perspective (i.e., "Here is what we found, and here is what the findings mean").

Policy and Historical Reviews. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and brief biographical sketch. Articles in this section include public health policy or historical reports that are based on research and analysis of emerging disease issues.

Dispatches. Articles should be 1,000–1,500 words and need not be divided into sections. If subheadings are used, they should be general, e.g., "The Study" and "Conclusions." Provide a brief abstract (50 words); references (not to exceed 15); figures or illustrations (not to exceed two); and a brief biographical sketch of first author—both authors if only two. Dispatches are updates on infectious disease trends and research. The articles include descriptions of new methods for detecting, characterizing, or subtyping new or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination programs are appropriate. Case reports are also welcome.

Commentaries. Thoughtful discussions (500–1,000 words) of current topics. Commentaries may contain references but no figures or tables.

Another Dimension. Thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit.

Letters. Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have one Figure or Table and should not be divided into sections. All letters should contain material not previously published and include a word count.

Book Reviews. Short reviews (250–500 words) of recently published books on emerging disease issues are welcome. The name of the book, publisher, and number of pages should be included.

Announcements. We welcome brief announcements (50–150 words) of timely events of interest to our readers. (Announcements may be posted on the journal Web page only, depending on the event date.)

Conference Summaries. Summaries of emerging infectious disease conference activities are published online only (effective January 2005). Summaries, which should contain 500–1,000 words, should focus on content rather than process and may provide illustrations, references, and links to full reports of conference activities.