

The global inter-relatedness of disease control

The Lancet Infectious Diseases has highlighted the crucial need to stress the global inter-relatedness of control of infectious diseases.¹ Control of vaccine-preventable diseases across borders is a key function of the regional immunisation programme of the Pan American Health Organization (PAHO).² PAHO's regional programme is grounded in the following core values: inter-country cooperation; capacity to identify problems and design appropriate solutions; capacity to sustain interventions; strong political commitment; sound programme management; national plans of action; well-functioning technical oversight and partner coordination; enhanced technical cooperation in high priority countries; cross-border cooperation; and the ability to respond to exceptional circumstances.

The outbreak that occurred in Venezuela between September, 2001, and November, 2002, was the last

instance of widespread measles virus circulation in the western hemisphere.³ However, sporadic cases and outbreaks associated with importations continue to occur after the disease has been eliminated (panel).

These measles outbreaks associated with importations draw attention to the tremendous challenge that PAHO and member countries have to protect and sustain the progress achieved in measles elimination in the Americas. In the post-elimination phase of measles control in the Americas, all these import-related outbreaks require an extraordinary amount of time and resources (both human and financial). Re-establishment of endemic measles virus circulation in the Americas upon importation remains a distinct possibility and would undo substantial progress in reducing child mortality, one of the eight UN Millennium Development Goals.

In September, 2003, the Directing Council of the PAHO adopted the resolution to eliminate rubella and congenital rubella syndrome in the Americas by the year 2010.⁴ This initiative was largely launched on the heels of the success of measles elimination. Keeping the region free of both measles and rubella will require continued actions to strengthen global cooperation of measles and rubella control, and will hopefully provide more lessons learned for an effective response to any pending global pandemic of influenza.

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We declare that we have no conflicts of interest.

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Panel: Sporadic cases and outbreaks that have occurred after the elimination of measles in the Americas

- In 2003-2004, Mexico reported outbreaks totaling 108 cases related to an H1 virus genotype indigenous to the far east and not the Americas
- In 2005, Brazil reported an outbreak of six cases related to an imported case infected in South Asia related to a D5 virus genotype
- From November, 2005, to February, 2006, Canada, Mexico, and the USA have reported cases related to a B3 virus genotype, a strain indigenous to central and western Africa
- The latest outbreak in Mexico has resulted in 27 confirmed cases and over 300 suspect cases have been investigated as of June, 2006. This outbreak has been limited to the metropolitan area of Mexico City (State of Mexico and Federal District); although an imported case could not be identified, the index-case patient was a baggage handler at the international airport of Mexico City
- From February, 2006, to present, Venezuela has reported 93 cases, the primary-case patient having a history of travel to Europe
- Most recently, the USA reported an outbreak of 18 cases in Boston related to an imported case likely infected in southeast Asia
- From October, 2006, until present, Brazil has reported an outbreak of 47 confirmed cases. D4 genotype was identified, indicating the source of the outbreak was most likely from Europe or Africa

Cholera vaccines

Despite more than 100 years of research, an effective vaccine providing long-lasting immunity against cholera has not been obtained.¹ A recent report on cholera vaccines has presented the topic from the perspective of travellers from industrialised countries visiting cholera endemic regions.² The report discussed a few oral cholera vaccines such as the whole cell, killed *Vibrio cholerae* O1 vaccine with and without the cholera toxin B subunit, isolated chemically (CTB-WC) or obtained by recombinant DNA technology (rCTB-WC), and a live attenuated CVD 103-HgR strain. The authors concluded correctly that cholera vaccines should not be used routinely in travellers because they are at extremely low risk of getting cholera.

Although David Hill and colleagues² identified young children to be very vulnerable to cholera, they overlooked some important publications, thereby presenting a biased view on cholera vaccines.^{3,4} A single-dose parenteral classical bivalent (Ogawa and Inaba) whole-cell vaccine with an adjuvant (aluminium phosphate) was subjected to a large-scale field trial in India in 1975.³ The vaccine offered 100% protection to children under 5 years of age for 6 months, 89% protection for 12 months, and 92% protection for 18 months. The overall protection rates for all age groups over a surveillance period of 1 and 2 years were 62% and 53%, respectively.

In Bangladesh, the three-dose CTB-WC containing a large mass of killed cells (37 times more than that contained in a parenteral vaccine) offered to all age groups a protective efficacy of 85% after 6 months during a period of sporadic cases of cholera epidemic.^{1,5} With the arrival of a cholera epidemic, protective efficacy fell to 58% at 12 months and was not different from that offered by the whole-cell vaccine alone.⁴ Upon analysis by age group, protective efficacy in children (2–6 years) was 38% after 1 year.⁴ At 14 months, the CTB-WC vaccine had a negative contribution to protection since 20–25% more children (3–6 years) in the CTB-WC group contracted cholera than those in the other groups, including the placebo control group.⁴ Furthermore, for children (2–5 years), protective efficacy was negative for CTB-WC (–37%) during the third year.^{1,6} These results suggest that the CTB-WC vaccine was not only ineffective in young children, but it increased the risk of cholera in the third year.^{1,7}

A non-randomised and non-placebo controlled Vietnamese trial of the two-dose spaced oral whole-cell vaccine showed protective efficacy of 68% in young children (1–5 years) at 8 months after immunisation.⁸ A single dose of the live attenuated recombinant oral vaccine offered little protection in any age groups in Indonesia.⁹ Therefore, among all the field-tested cholera vaccines, the single-dose parenteral whole-cell vaccine with adjuvant tested in India had provided the best protective efficacy for young children against cholera.³ These crucial pieces of information were not addressed by Hill and colleagues.²

Cholera vaccines, whether live or dead, administered orally or parenterally, can cause side-effects. The oral cholera vaccines tried in Bangladesh and Latin America had induced adverse reactions such as stomach pain, nausea, headache, swollen throat, mouth lesions, diarrhoea, vomiting, and fever in the recipients.^{1,10,11} Parenteral killed whole-cell vaccines, with or without the adjuvant, are well tolerated and can produce side-effects that do not limit the activity of the vaccinees,^{3,12} however, these side-effects have been exaggerated.^{12,13} Various criticisms of parenteral killed whole-cell cholera vaccines have been adequately rebutted in an in-depth systematic review covering 17 trials during 1963–1971 that tested parenteral killed whole-cell vaccines in 1.5 million people in several cholera endemic countries.¹² Single-dose parenteral killed whole-cell vaccines were introduced in India in the 1930s as a cholera prevention measure and a substantial decline in the number of fatal cholera cases was achieved.¹⁴ Furthermore, extensive observations from the field trials in Bangladesh covering five cholera seasons demonstrated that a considerable degree of protection is achievable from a vaccination programme repeated annually.¹⁵ Therefore, the logic of abandoning parenteral killed whole-cell vaccines, thereby depriving people of a relatively effective and inexpensive cholera vaccine, has been questioned.¹²

The oral cholera vaccine CTB-WC/rCTB-WC, sold as Dukoral, is very expensive.¹⁷ The vaccine delivery system is inconvenient, requiring stomach acid neutralisation, which can be problematic for people with stomach ailments. Various factors such as short-term efficacy, poor protection in younger children, necessity for multiple spaced doses, reduced protection against El Tor



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cholera, cold chain requirements, and very high cost make it unsuitable for routine use in cholera endemic countries where an economical cholera vaccine offering a high degree of long-term protection is needed.

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I declare that I do not have any conflicts of interest.

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Authors' reply

Shahjahan Kabir raises important issues regarding the usefulness of cholera vaccines in endemic settings and particularly in children younger than 5 years. We certainly agree that there is a need for an effective, easily administered vaccine to prevent all *Vibrio cholerae* serogroup infections in those most vulnerable to the effects of cholera. The focus of our paper, however, was the use of oral cholera vaccines in travellers and not the use of vaccine to control cholera in endemic regions. There are many studies that report on the efficacy of injectable inactivated vaccines; these demonstrate variable efficacy depending upon the country where the trial was done, the vaccine composition (including whether or not adjuvants were used), and the age of the population vaccinated. Rather than analysing some or all of them individually, as was done by Kabir, we referred to review articles or chapters.^{1–3}

WHO has concluded that killed parenteral vaccine does not prevent transmission of cholera and the efficacy is modest and of short duration, and therefore this form of vaccine should not be used in endemic settings.⁴ WHO also recognises the potential use of oral vaccine in some endemic and epidemic situations to complement existing control strategies.^{4,5}

Unfortunately, options for the control of cholera in endemic regions require expensive and complex strategies.⁵ Travellers usually have the advantage of being able to pay for what may be costly interventions, including vaccination. The goal is to bring effective interventions in a cost-effective manner to the resource-poor regions of the world where they are most needed.

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Unsafe medical injections and HIV transmission in India

We read with great interest Padma Chandrasekaran and colleagues' comprehensive review of the HIV/AIDS epidemic in India.¹ We would additionally like to emphasise the role of increasing the regulation and accountability of the medical sector in containing the epidemic.

India's health system remains dominated by a largely unregulated private sector that accounts for greater than 80% of domestic health expenditures. Owing partly to the low trained doctor-to-patient ratio, unqualified "quack" practitioners provide the bulk of clinical care to the poor, particularly in rural areas. The result has been that unsafe injections remain extremely common throughout the country.²⁻⁵ A survey conducted at our centre in northern India showed that 35% of citizens in one rural village had received some form of medical injection in the past 6 months, most of which were given by an untrained medical practitioner.⁴ Data from our National AIDS Control Organization (NACO)-supported antiretroviral clinic have shown that for approximately 3% of patients the only identifiable source of HIV infection is through unsafe medical injections. In view of the high prevalence of receipt of unsafe medical injections among high-risk marginalised groups in particular,³ these injections may contribute to the spread of HIV both within high-risk groups and between high-risk groups and the general population.

To combat the small but significant ongoing transmission of HIV via unsafe medical injections, it would be wise for NACO to incorporate the following strategies into its comprehensive control programme. First and foremost is strengthening and expanding public sector primary medical care. Comprehensive AIDS control cannot occur in the absence of a strong public

sector capable of meeting the basic medical needs of the poor. The private sector has proven woefully inadequate and dangerous in this regard. By meeting these needs, the use of quack practitioners will decrease. Second, expanding the use of auto-disable syringes would help to decrease the secondary use of contaminated needles by medical providers.⁵ Finally, concrete steps need to be taken to increase governmental and self-regulation of medical practice, in both the private and public sectors.

The rapid expansion of HIV/AIDS in India is a symptom of a larger disease: the failure of the public provision of health care to vast swaths of the nation's poor. The persistent transmission of HIV by unsafe medical injections is but one manifestation of this failure. While the prescriptions laid out by Chandrasekaran and colleagues are crucial and immediate steps to take, we must also remain cognisant of the broader health systems perspective if we are to truly stop HIV.

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Tuberculosis patients: some don't...some do, some won't... some will

We read with interest the International Standards for Tuberculosis Care (ISTC) published in the November, 2006, issue of *The Lancet Infectious Diseases*.¹ Focusing mainly on essential activities that all practitioners—public and private—should endorse regarding the

management of patients diagnosed with suspected or confirmed tuberculosis, the ISTC brings to the forefront the responsibilities of all providers in delivering quality care to their patients. However, of equal interest is the publication of the Patients' Charter for Tuberculosis

Care,² which addresses the rights and responsibilities of patients diagnosed with tuberculosis and which was developed in tandem with the ISTC.

In tuberculosis control we have much experience with patient non-adherence and of the issues surrounding a patient's inability or unwillingness to follow through on programme directives. As a result, we have become undaunted by the reality that patient non-adherence is commonplace in the world of tuberculosis. However, it also should be acknowledged that patients who often demonstrate adherent behaviour are rarely discussed and virtually never reported. The following case report is of a patient's remarkable determination to keep his scheduled appointment in an out-patient tuberculosis clinic and demonstrates how his actions may serve as a symbol of the Patients' Charter for Tuberculosis Care.

On July 5, 2005, a male patient submitted to a medical examination in Taiwan for travel clearance to the USA. Diagnosed with inactive pulmonary tuberculosis, he arrived in New Jersey in November, 2005. After visiting with relatives for 1 week, the patient decided to return to Taiwan. Because of unspecified delays, immigration papers were forwarded to the local tuberculosis control jurisdiction in March, 2006. Unaware that he had already returned to Taiwan and believing that this was a recently arrived immigrant, the local tuberculosis programme initiated a field investigation to begin the process of locating and referring the patient for medical evaluation. Field visits proved unsuccessful in contacting this individual. A certified letter was posted informing him of an appointment for April 28, 2006. On the appointment date, the patient appeared at the clinic.

A chest radiograph taken that day was negative. Accompanying the patient were English-speaking

relatives who acted as interpreters. During discussions between the physician and interpreters, the patient's US travel history emerged. It was revealed that not only did he return to Taiwan in November, but he remained there until the day before his scheduled clinic visit in New Jersey when, as requested in the certified letter forwarded by his family in the USA to Taiwan, he flew from Taiwan to Newark to keep his appointment at the tuberculosis clinic. Profuse apologies were offered to the patient for the inconvenience and unfortunate misunderstanding that had occurred. When asked why he felt the need to fly to the USA to keep his appointment the patient replied "because it sounded important".

So the thought that lingers is how interesting it is that someone could justify flying 24 h from across the world to keep an appointment at a tuberculosis clinic whereas someone else living across town can justify reasons for not keeping an appointment. This is an extreme example of adherence but one that perhaps makes the more typical excuses offered by non-adherent patients seem quite shameful.

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We declare that we have no conflicts of interest. MW and LR are supported by both the New Jersey Department of Health and Senior Services, and the Centers for Disease Control and Prevention.

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