Cholera

Forget vaccines this time around

The current cholera epidemic in Peru and Ecuador is the first exposure of the South American continent to the forecast extension of the seventh cholera pandemic, which started in Indonesia in 1961 and has passed through Asia, the Middle East, Africa, southern Europe, and Japan (p 1039). In Peru the estimated attack rate for cases of cholera is 2%, and within the next six weeks an expected 200 000 people are likely to become infected. Despite the major advances in managing diarrhoea with oral rehydration therapy, pioneered during previous cholera epidemics in Asia, a 1% case fatality rate from dehydration is forecast during this period.¹ The *Vibrio cholerae* 01 biotype El Tor migrates by human carriage along trade and travel routes; when infection occurs severe diarrhoea develops in 2-5% of cases, while three quarters of infections are subclinical. To put cholera in perspective, during an epidemic it accounts for less than 5% of acute diarrhoeal episodes in a community. Healthy carriers of the El Tor vibrio have been recognised as an important catalyst in the spread of cholera and are capable of excreting viable organisms for around five days after infection.^{2,3} Surveillance and microbiological screening of travellers from infected areas would need to be mandatory but are highly impractical.

Control of cholera epidemics depends on some cardinal principles: isolate, treat, and render cases non-infectious; monitor and treat contacts; establish and enforce environmental sanitation; protect and treat drinking water and food, especially fish, and avoid contaminated vegetables; and use oral rehydration salts, which are effective in managing 90% of outbreak cases. Cholera is a disease of slums and poverty, and resources needed to implement a control programme require political and economic support. Mandatory vaccination of travellers as a strategy to control the spread of cholera may be tempting, but can lessons be learnt from previous attempts at curbing cholera's invasion?

The clinical presentation of El Tor cholera is of a mild diarrhoeal illness, unlike the more profuse diarrhoea associated with classic cholera.⁴ As part of the international effort to control the spread of diseases the World Health Organisation's international sanitary regulations were replaced with international health regulations in 1969, making evidence of immunisation against cholera a legal requirement for people travelling from a region where cholera was endemic.⁵

Although humans are the only important carrier of *V. cholerae*, some countries imposed extreme measures—for example, placing aircraft passengers in quarantine, disinfecting surface mail and airmail, and prohibiting the importation

of tinned foodstuffs.⁶ Surveillance and monitoring of cholera depended on international reporting and scrutiny of the immunisation status of travellers at sea, air, and road ports of entry. Most cases that were introduced into non-infected regions occurred despite intensive surveillance; illegal immigrants and small unsupervised ports were usually to blame.

The phenol or heat inactivated parenteral cholera vaccine on which this control strategy was based was shown in field studies to provide 50% protection for an average of three months and has virtually no role in controlling cholera epidemics. Measures incorporating sanitation, personal hygiene, and safe water are much more important.⁷ Having had little impact on the worldwide dissemination of cholera, the strategy of vaccination was rescinded by the United States Surgeon General in 1971 and WHO in 1973.⁵ WHO's current international health guidelines do not recommend immunisation for preventing the introduction of cholera into a country and state that it should not be required of any traveller.⁸

Establishing the risk of cholera to a traveller is difficult, but over 20 years in the United States 10 cases of cholera were notified from an estimated six million travellers to areas with endemic cholera. Details were available on only eight cases; in four full vaccination had been given within the previous six months—confirming that immunisation confers poor protection.⁹ In Britain over the same period 66 cases of cholera were reported to public health laboratory services (Communicable Disease Surveillance Centre, personal communication). Calculations of attack rates in visitors to tropical countries can be estimated from data on the total numbers of British travellers derived from the international passenger survey. They suggest an incidence of one in 800 000 in 1986 and one in 210 000 in 1989, a rate not dissimilar to that seen in American travellers.

Serious risks associated with parenteral cholera immunisation are rare, but anecdotal reports include sudden death, stroke, and transverse myelitis after the administration of combinations of cholera and typhoid vaccines. Recipients may perceive immunisation against cholera protecting them against all diarrhoeal illnesses, and this misconception may be the greatest disadvantage of any immunisation procedure against a diarrhoeal illness. With travellers' diarrhoea affecting 20-50% of travellers to the tropics,¹⁰ advice about diet and treatment, especially oral rehydration, should be given priority over immunisation.

In 1989 the cost to the NHS of 221 000 prescriptions for cholera vaccine was around £850 000, excluding the costs of

non-prescription doses and administration (Department of Health). Part of the explanation for the widespread use of cholera vaccine was recently highlighted in a study of the prescribing practices of British general practitioners. Nearly three in four general practitioners would immunise travellers to the tropics, giving reasons such as the risk of cholera, fear of litigation, need for certification, and advice from expert sources. The study also highlighted the disparate opinions on the indications for cholera vaccination from various travel health information sources.¹¹ Another undoubted influence on prescribing is the demand of some border health officials for evidence of cholera certification as a prerequisite for entry to a country. This practice continues covertly, disrupting many a traveller's passage. Vaccination at the port of entry may be risky: one traveller developed hepatitis B after he was vaccinated by a border official to satisfy local requirements on cholera.¹² WHO advises that official cholera certification is not a legal requirement for international travel and on no account should travel be restricted because of cholera.¹³

Until WHO's agreed entry requirements on cholera immunisation are enforced by WHO signatories, consistent and effective advice on indications for cholera vaccination are not feasible. Replacements for the parenteral vaccines are currently being evaluated, and field trials of an orally administered killed whole cell *V. cholerae* vaccine combined with a B subunit peptide suggest it provides comparable protection to that provided by the parenteral form.¹⁴ Results of studies on the efficacy of live oral cholera vaccines are

awaited. The risks of cholera or associated morbidity are so low, however, that the cost-risk benefit of any vaccine must be carefully considered before it is widely adopted for use in travellers.¹⁵ The protection of travellers against diarrhoeal illnesses is unlikely to advance greatly until vaccines against enterotoxigenic *Escherichia coli* become available.

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An NHS research strategy

Overdue but potential problems with implementation

For the first time in its history the NHS has a research strategy. It was announced last week, three years after the House of Lords Select Committee on Science and Technology advocated that "the NHS should be brought into the mainstream of medical research."¹ The committee asserted that no research system could work effectively when the principal customer had so small a direct input into the initiation of research programmes. "The needs of the NHS and its problems," argued the committee, "will be met only if those needs are clearly expressed. The needs are not expressed."

The solution proposed by the House of Lords committee, an NHS research authority, appealed to very few—not least because special health authorities have an undistinguished history. Instead, the government proposed appointing a director of research and development, who would sit on the NHS Management Executive. Professor Michael Peckham, director of the British Postgraduate Medical Federation, was seconded to the post in January and has now cleared his strategy through the management executive and the Secretary of State for Health.

Many strategies fail because they do not start by analysing the current position of an organisation. Recognising this, Professor Peckham and his team began by surveying the existing health research effort. This is no mean task because it is so fragmented, but the team estimates that altogether Britain spends something like £1.5 billion on health research. Even with a health service budget of £30 billion this seems a reasonable sum to spend on research. But most of the money is spent by industry, much of it on routine toxicological

studies. The Medical Research Council's budget is about £200m a year, and the Department of Health spends something like £225m—through SIFTR (service increment for teaching and research), locally organised research schemes, special health authorities, the former department of the chief scientist, and organisations like the National Radiological Protection Board and the Health Education Authority. To the annoyance of an incoming director, most of this money is spoken for, although by bringing it into the new research and development framework it might eventually be redeployed.

How much should be spent on health research? It is hard to find an answer from industry or other countries, but Professor Peckham believes that the NHS should be spending about 1.5% of its turnover. This would mean something approaching £400m. This, believes Professor Peckham, is a reasonable amount because the service is desperately short of information, performing many expensive and unvalidated procedures, and ultimately driven by new technologies and scientific developments. Few technological industries would spend as little as 1.5%, and successful research based industries—like the pharmaceutical industry—spend as much as 10% of their turnover on research. Despite these arguments £400m is a large sum for a cash starved service to spend—but the management executive has accepted the sum in principle.

The content of the NHS strategy will include clinical and health services research, and Professor Peckham believes that these are "two sides of the same coin." Also important will be the development part of research and development,