Editorial

A new era in the history of cholera: the road to elimination

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Historical background

One hundred and fifty years ago, Snow made the historic discovery that contaminated water transmitted cholera, but there were many other key discoveries and notable developments in the history of cholera. Koch cultured V. cholerae, the bacterium about which Snow could only speculate, and S.N. De discovered the enterotoxin produced by the bacterium resulting in massive outpouring of fluid. But these discoveries, by themselves, did not save the lives of cholera’s victims; 50% of them died until intravenous hydration therapy began to be used by Rogers in the early 1900s. This hypertonic intravenous solution reduced the case fatality rate, but not until the late 1950s and early 1960s were consistently successful treatments implemented based on careful intake and output balance studies.

The Watten cot

An especially important innovation, often taken for granted today, was the development of the ‘Watten cot’ which is now used routinely in cholera treatment centres worldwide. Watten first conceived this simple army cot with a hole in the middle onto which a cholera patient was placed. A plastic sheet funneled the watery stool through the hole into a bucket under the bed, allowing for accurate measurement of stool output. Studies in Bangkok, Calcutta and Dacca used this cot to determine the volumes and chemical composition of cholera stools and ushered in a change in the basic concept about the treatment of cholera: the diarrhoea fluid that is expelled must be replaced by rehydration fluids in volumes and chemical composition to match that being lost. The Watten cot, originally used for these physiological balance studies, is now the standard of care and is used throughout the world for millions of patients with severe diarrhoea.

Proper rehydration

Other major developments in cholera’s history include the perfection of the composition of the intravenous fluid using Ringer’s lactate or, even better, the cholera solution used in Bangladesh, and the use of appropriate antibiotics to shorten the illness and lessen the purging rate. Critically important was the observation that glucose mediated sodium transport in the gut during cholera illness. This insight led to the development of oral rehydration solution which has saved the lives, not just of cholera patients, but of millions of children with non-cholera diarrhoea.

These improvements in treatment led to a reduction in case fatality rate to nearly zero, at least for the patients who were able to reach a high quality treatment centre. Meanwhile, improved water and sanitation virtually eliminated the risk of cholera in industrialized countries, and it appeared that the cholera problem had been solved. The illusion of cholera’s disappearance as a public health problem was reinforced by the lack of reporting from many countries which actually had endemic cholera. The relative importance of cholera was further downplayed by the understanding that many more children were dying of ‘ordinary diarrhoea’ than cholera, so the emphasis shifted away from cholera to addressing the more pressing issue of children’s non-cholera diarrhoea.

The global spread of cholera

Unfortunately, cholera cases and cholera deaths did not stop. In fact, the seventh pandemic, El Tor cholera spread through Asia, then to Africa in 1970s and then on to Latin America in the 1990s. Cholera now persists in Sub-Saharan Africa leading to outbreaks which have become more frequent and more severe in recent years. Fortunately, the epidemic in Latin America, after spreading through most of the continent has subsided, and no cholera has been reported in recent years from South or Central America.
Surprisingly, the 1991 Latin American epidemic did not spread to Haiti or the Caribbean Islands, but in October 2010 the Asian strain appeared along the Artibonite River in Haiti.14 Regardless of how it arrived in Haiti, the conditions were ideal for its rapid spread to the entire country, leading to over 700,000 cases, over half of whom were hospitalized, and 8000 deaths.15 The devastating epidemic in Haiti, which has now spread to Cuba and recently to Mexico, dramatically demonstrated how dangerous cholera can be, and this epidemic, so close to North America, has raised cholera’s profile but has also led to a more concerted and coordinated effort to control the disease, not only in Haiti but in Africa and Asia as well.16

About 2.8 million people are estimated to become ill with cholera each year, and since asymptomatic infections are common, 5 to 10 times as many are infected. The world death toll is estimated to be over 100,000 annually,17 although only a fraction of these are reported. To deal with this global threat in Asia, Africa and the Caribbean, the strategy to control cholera has primarily focused on WASH interventions (improved water, sanitation and hygiene) and ensuring proper case management with hydration and antibiotics. These interventions are critical to the eventual control of cholera, but clearly they have not been sufficient. Populations most at risk of cholera are unlikely to have safe water and improved sanitation for many decades. Although ‘point of use’ water treatment provides protection when used properly, this has been difficult to sustain on a large scale, and drinking pure water does not negate the risk from contaminated water which may also be consumed.18

Oral vaccines

Will vaccines be the answer to preventing and controlling cholera? Killed whole-cell injectable vaccines were discarded by the early 1970s because their short duration of protection and their reactogenicity made them unsuitable for public health use. Nevertheless, vaccine research continued, leading to the manufacture of licensed safe and effective oral vaccines including Dukoral, Shanchol, mORC-Vax and Orochol. Dukoral, the first oral cholera vaccine to become available, is composed of killed whole cells of V. cholerae serogroup O1, plus the binding, nontoxic subunit of cholera toxin. This vaccine stimulates an intestinal immune response to both the bacterium and the enterotoxin. Shanchol and mORC-Vax are similar to Dukoral except that they do not include the binding subunit, but they do include killed whole cells from the other toxigenic V. cholerae, serotype O139. Both Dukoral and Shanchol are prequalified by the World Health Organization (WHO)—a process to determine the acceptability, in principle, of vaccines from different sources and allow for procurement through the United Nations system. Orochol differs from the other oral vaccines, being a live attenuated oral vaccine. It was licensed in the past, but is not currently available. There are plans to reintroduce this vaccine, under a new name.

Among these currently available vaccines, Shanchol seems most suitable for public health use because of its relatively lower cost ($1.85 per dose), its simplified distribution and administration and its WHO prequalification. Shanchol has now been given to over 1 million people in campaigns in several countries including Haiti, Guinea, South Sudan, India, Bangladesh and Thailand, and it is now becoming available through a stockpile administered by WHO. There is growing enthusiasm that the appropriate use of Shanchol, or a similar vaccine, when used along with WASH, quality case management and other interventions, will dramatically reduce the threat of cholera for populations at risk. Assuming that oral cholera vaccine is now becoming increasingly available, how will vaccine be used appropriately and what other interventions will be needed to truly turn the tide on cholera without waiting for universal modern water and sewage systems? Can cholera ever be ‘eliminated’ or ‘eradicated’ as is now being discussed for malaria? Perhaps some lessons from malaria are appropriate in this discussion on cholera.

Cholera and malaria

In 2007, when the Gates Foundation called for a new global commitment to chart a course for malaria eradication, many (if not most) tropical medicine experts thought that this was totally unrealistic and an impossible goal.19 The earlier failed efforts toward eradication discouraged most of them from even mentioning the word ‘eradication’. Today, many of those sceptics are contributing to identifying new strategies, medicines, diagnostics and vaccines, towards the goal of elimination if not eradication.20 Have these researchers and public health professionals joined this eradication effort simply because it has opened new sources of funding for their work, or do they truly believe that eradication is possible? Regardless of the motivation, the call for malaria eradication has invigorated new thinking, innovative approaches and the attempt to integrate technologies in ways that were not possible before. Malaria ‘eradication’ is still a long-term goal, but many countries are achieving significant reductions in malaria rates and malaria mortality, and 34 countries are now considered ‘malaria-eliminating’ countries.21

According to Feachem, a malaria-eliminating country is one that ‘has formally declared a national, evidence-based elimination goal, has assessed its feasibility, and has embarked on a malaria elimination strategy’, and is ‘a country that is strongly considering an evidence-based national elimination goal, and that has already made substantial progress in spatially progressive elimination (e.g. by eliminating
malaria from specific islands, province, or geographic areas) and in greatly reducing malaria nationwide.\textsuperscript{22} By contrast, a ‘controlling country’ is one where interventions have reduced endemic malaria transmission to such low levels that it does not constitute a major public health burden, but at which transmission would continue to occur even in the absence of importation.\textsuperscript{22}

Controversies continue about the exact meaning of extinction, eradication, elimination and control,\textsuperscript{25,26} but there is now optimism that malaria can at least be controlled and even eliminated in some regions of the world where it has formerly been a major threat. If there is hope for malaria, is it time to consider ‘elimination’ for cholera?

At first glance, malaria and cholera seem to be totally unrelated diseases, one being a vector-borne blood parasite, the other being a water-borne, intestinal bacterial disease. But they also share many similarities including a similar global geographical distribution, seasonal epidemic patterns, the importance of ‘hot spots’ and the risk of re-introduction from neighbouring areas. Both are also highly dependent on the ecology of water (Anopheles larvae and \textit{V. cholerae} both depend on local bodies of water). A major difference is that \textit{V. cholerae}, being part of the ‘normal flora’ of environmental water, can persist independently without human infection,\textsuperscript{24} whereas malaria has no such non-human reservoir. Although this suggests that there is no chance for true cholera eradication, it does not mean that human-to-human transmission cannot be eliminated and that the disease could not be eliminated as an epidemic threat.

**Eliminating cholera as a public health problem**

Although recognizing the differences in the biology of the two infections, if one emulated the approach from malaria by setting a goal for cholera’s elimination, one wonders what new and innovative ideas would emerge. Using the example from Feachem, a cholera-eliminating country might be one that formally declares a national, evidence-based elimination goal, has assessed its feasibility, has embarked on a cholera elimination strategy and is committed to making substantial, time-bound progress in spatially progressive elimination.

If a country aspires to become an eliminating country, it will need to use all the tools available and be alert to the potential for other newer approaches. In the absence of a magic bullet, the tools will certainly need to include at least the following components: (i) improved case management to insure that no cholera patient dies; (ii) an epidemiologically valid surveillance system for all areas of the country, especially remote vulnerable areas; (iii) the intelligent use of oral cholera vaccine among high risk groups; (iv) short- and long-term strategies for safe water and improved sanitation; (v) monitoring, evaluation and research activities to continually improve the programme; and (vi) an effective communication programme stressing the coordination of these different components in the communities affected.

Controlling cholera implies reducing transmission such that the reproductive number is reduced to less than one.\textsuperscript{25,26} By definition, in cholera endemic areas, the reproductive number exceeds this number during outbreaks. However, the finding that oral vaccine induces substantial herd protection\textsuperscript{27} demonstrates the ability of vaccine to reduce the reproductive number by reducing vibrio environmental contamination. With less vibrio contamination, the effectiveness of WASH activities should also improve. It has been impossible to achieve 100% compliance with home water treatment, but if/when some contaminated water is consumed, it would be helpful if everyone was immunized so that the water, even though it may be faecally contaminated, does not contain large numbers of \textit{V. cholerae}.

**A new era for cholera**

Is a goal for elimination unrealistic? The alternative is to simply hope that some day modern infrastructure will deliver safe water to everyone and to rely on the best treatment for patients who continue to become ill. Hopefully, the public health community will utilize oral vaccine as an opportunity to initiate a new chapter in the history of cholera. This could occur, not only because of the biological effectiveness of the vaccine itself, but because the vaccine will usher in new hope with innovative thinking about cholera’s elimination. The success of the current vaccine, Shanchol, should stimulate the development of even more cost effective vaccines that can be manufactured and distributed more efficiently. Since countries will need to learn when and where to use vaccine, they will need to establish sentinel surveillance systems. These will likely need to use validated rapid tests suitable for remote areas in order to detect cholera outbreaks earlier, understand its seasonality and define its hot spots. Endemic countries which do not currently report cholera should become more transparent about their cholera burden, to determine where to use vaccine to benefit their people. Microbial surveillance of surface water will improve early warnings, and routine microbial monitoring of municipal water for \textit{V. cholerae} will alert city officials. The improved surveillance will also benefit WASH activities which may more effectively focus on specific times and places of highest risk. Cellphones, social media and mass media will assist vaccine campaigns (similar to influenza messages in the USA) and reinforce effective WASH messages. Importantly, eliminating countries will exchange information about their
attempts to control cholera and they will learn from each other what works and what does not. Many of us look forward to this next chapter in cholera’s history; hopefully this will be the last one.

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References