Pathways to a policy for cholera control in India

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A B S T R A C T
Cholera is endemic in southern Asia, but available control mechanisms have either not been applied or have been ineffective. Oral killed cholera vaccines are now available, are pre-qualified by the World Health Organization (WHO) and are being stock-piled by the Gavi Alliance. Although cholera vaccines have been tested, manufactured and licensed in India for several years, they are not in use in public health programmes for either endemic disease or outbreaks. The National Technical Advisory Group on Immunization (NTAGI) is the advisory body that considers disease burden, vaccine performance, cost-effectiveness and potential for introduction into national programmes, reporting to the Ministry of Health. The NTAGI also takes into account the recommendations of the WHO and is now considering cholera vaccines. Policies for cholera control are urgently needed, and the availability and affordability of an oral cholera vaccine in India offers new opportunities to control an important public health problem.

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1. Introduction

If cholera can be said to have a home, it is in the coastline of the Bay of Bengal. In this area of southern Asia, cholera is both an endemic and an epidemic disease and has been recorded in history as a distinct, recognizable condition that was frequently fatal. Over the last two centuries, cholera pandemics have taken the disease to multiple parts of the world, where outbreaks continue to happen in locations where safe water and adequate sanitation have not been ensured. In the Gangetic delta, cases are particularly prominent after the monsoons, reaching numbers that can overwhelm the capacity of hospitals to deliver rehydration [1].

While health practitioners at all levels in India recognize the distinct clinical presentation of cholera, not many cases of cholera are reported from the regions that are known to be most affected. For endemic disease, although cholera is a notifiable disease, there are few reports from public or private facilities. The Integrated Disease Surveillance Program (IDSP) coordinated by the National Centres for Disease Control, under the Ministry of Health and Family Welfare (MOHFW), Government of India, reports on outbreaks and while cholera is now being reported occasionally, many outbreaks continue to be considered as acute watery diarrhea of unknown aetiology [2]. For both endemic and epidemic disease, this is frequently because testing is not done, or because public health authorities are unwilling to admit that their region has cases of cholera.

Understanding the biology of Vibrio cholerae and the epidemiology of cholera are important for designing control measures and predicting the potential for impact. The environmental reservoir in saline estuaries and in zooplankton and shellfish explain the endemicity of cholera in the Bay of Bengal [1], but endemic disease in areas remote from the coast in India is less well studied, with only a few reports of detection of non-cultivable vibrios in inland water bodies and limited correlation with disease [3,4].

2. Decision-making for control of cholera

Given the burden of disease, it is important for public health authorities in southern Asia to consider options for the control of cholera in multiple settings. In India these authorities are the MOHFW at the centre and in states. The MOHFW liaises on health related matters with multiple stakeholders in health and other fields, including ministries that supervise sanitation, water, women and children, finance, etc, as well as professional bodies of the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders. With regard to the potential use of vaccines, the MOHFW is advised by the National Technical Advisory Group on Immunizations (NTAGI) [5], which is chaired by the Secretary of the MOHFW. While ultimately a decision made by the Ministry, the government prioritizes its policy after considering the recommendations of the NTAGI. The NTAGI’s technical inputs come from the scientific community, civil society and opinion leaders.
Biotechnology, and has independent and ex-officio technical experts in pediatrics, infectious diseases, microbiology, epidemiology, public health, etc.

2.1. Cholera disease burden

Magnitude and distribution of disease are important considerations in deciding if a disease constitutes a health priority. Unfortunately very often, good quality data on burden of disease is unavailable when a decision on vaccine introduction is considered. In the case of cholera, there are social and other considerations partially determining whether cholera is reported in a region. Creating nationally representative population based surveillance systems to monitor diseases is therefore an investment each country should consider. In India, at least for outbreaks, the IDSP has been reporting outbreaks, although as stated previously, aetiology is not often determined. In the case of endemic cholera, because of the environmental drivers of disease, the disease tends to be seen in specific locations and populations, and targeted surveillance may be feasible [6].

While active surveillance is expensive, passive surveillance which relies on clinicians, hospitals or laboratories reporting cases routinely is a cost-effective way to collect data. Clinical case definitions can be applied and need laboratory confirmation of aetiology. However, with facility based capture, data quality and completeness are issues to consider, incidence rates will not be available, and it may not be possible to obtain rates of hospitalization and proportional mortality, which are measures of disease burden.

The consequences of a disease in terms of mortality, morbidity and long-term disability also matter. Although cholera is an acute disease, it has the potential to be fatal if there is lack of access to a healthcare facility, with case fatality rates reported to be up to 50% in some outbreaks [7]. Multidrug-resistant and El Tor cholera are associated with more severe outcomes, longer hospital stays, and higher case fatality rates. Economic implications of hospitalizations and acute medical care are also measures of burden. Additionally, prioritization for governments may result from other drivers. For example, diseases associated with greater transmissibility, rapidly create awareness and result in greater media coverage and therefore may become priorities for the government.

When indigenous disease burden data is unavailable, policy makers may rely on data from similar regions, or consider mathematical models. Data from mathematical models on burden should be interpreted cautiously as a variety of underlying assumptions can influence the estimates.

Equity and social justice are important determinants for which populations are likely to benefit most from interventions. Since cholera disproportionately affects vulnerable populations, it should be a public health priority.

2.2. Choice of interventions

Interventions for cholera are available, and consist of options for prevention and for treatment to manage cases, prevent adverse outcomes and prevent further transmission. Safe water and sanitation were responsible for the control of cholera in the industrialized world [1], and are likely to be contributing to the decrease in cases in some regions of the Indian subcontinent. However, whether officially reported or not, cholera continues to occur in southern Asia, with a periodicity which could lend itself to effective control measures.

Cholera vaccines were among the first vaccines to be tested in Asia well over a century ago, with large trials of both parenteral and oral vaccines, but reactogenicity, low efficacy and high cost restricted their use. In the past decade, low-cost killed oral cholera vaccines (OCV) have been developed, and evaluated in India and Bangladesh [8]. A recent systematic review has reported that with two doses of vaccine, efficacy is about 58% (95% CI 42–69) and effectiveness 76% (95% CI 62–89), with protection lasting up to 5 years. The efficacy and effectiveness did not appear to differ between the more expensive killed OCV with the B-subunit and the cheaper bivalent killed OCV without the B-subunit [8].

Despite the availability of multiple interventions to control cholera, vulnerable regions such as those with poor environmental conditions, unsafe water and inadequate sanitation continue to be affected by cholera. Disruptions of populations by natural disasters, wars and internal displacement, lead to the concentration of large numbers of people in poor sanitary conditions, and consequent exposure to cholera.

Historically, cholera control has depended on improvements in water and sanitation, which have performed well in industrialized countries, wiping out cholera outbreaks. In India, according to the UNICEF and WHO Joint Monitoring Programme of progress in drinking water and sanitation, access to improved sanitation improved from 49% in 1990 to 63% by 2015 while in rural areas the change was from 6% to 28% over the same time period. Similarly, access to piped water increased from 47% in urban settings in 1990 to 54% in 2015 and in rural areas the increase was from 6% in 1990 to 16% by 2015. However, it has also been estimated that halving the number of people globally who do not have access to improved water and sanitation will cost 11.3 billion US dollars annually [9]. The costs of significantly improving water and sanitation immediately across India may be large, but this is a goal towards which progress will continue to be made, especially through programmes like the Swachh Bharat Abhiyan.

When considering vaccines as a potential preventive intervention, several factors influence the decision making process. First, introduction of vaccines into a national immunization programme helps equitable access, since vaccines targeted at infectious diseases that affect the economically disadvantaged are most likely to have the greatest impact on disease as the poor have limited access to curative healthcare services. An ideal vaccine is one that is highly effective, without any adverse effects, easy to store, transfer and administer, administered within current immunization schedules, readily available, cheap and produced within the country. Such vaccines with high efficacy and safety and low cost are rare. In the case of cholera vaccines, the oral cholera vaccine that is made in India is inexpensive, effective and easy to store and administer, but its requirement for two doses with an interval of 14 days poses a challenge, since this does not fit in the routine immunization schedule.

In countries with large health care needs, vaccines must compete with other alternatives both in terms of the disease and with regard to the intervention. Cost-effectiveness studies as well as evaluation of alternate strategies for control are critically important to make these decisions, and are not always available in developing countries. For cholera, cost-effectiveness analyses have been carried out and demonstrate that in areas of high burden, the use of the vaccine is cost-effective. A study from Bangladesh showed that the oral vaccine was highly cost-effective when targeting ages 1–14 y, and cost-effective when targeting ages 1+y, in high-burden/high-risk districts. Other strategies for vaccination targeting areas without improved water were also found to be cost-effective [10]. The vaccines were also cost-effective in India, when herd protection was included [11].

2.3. WHO recommendations on oral cholera vaccines

The WHO published a position paper on cholera in 2010, which had recommended two doses of a killed oral bivalent cholera vaccine two weeks apart in those aged over one years, with booster doses after two years [8], is now updated with the 2017 recom-
mendations of the Strategic Advisory Group of Experts (SAGE). SAGE has recommended that cholera vaccines need to be considered in three settings, (i) endemic cholera, (ii) humanitarian crises with a high risk of cholera and (iii) outbreaks. In all settings, the use of vaccination must be in conjunction with other activities including appropriate case management, water, sanitation and hygiene interventions, surveillance and community mobilization. Most supplies of cholera vaccines are currently expected to come from the Gavi Alliance stockpile, and it is recommended that countries and agencies accessing the stockpile conduct monitoring and evaluation activities to monitor impact, effectiveness and cost-effectiveness in different settings and age groups. Pregnant women and frontline healthcare workers are recommended to be included in vaccination programmes.

For endemic disease, classified as confirmed cases in three of the previous five years and evidence of ongoing transmission, cholera vaccination should be taken up in priority areas or groups. Both vaccine purchase and the delivery strategy should be budgeted by the health ministry. In humanitarian emergencies, a risk assessment should determine the need for vaccination and the populations to be targeted. In outbreaks, a single dose strategy may be considered for short-term protection. The SAGE also identified several key areas, particularly on herd protection, where further research is needed.

In conjunction with the updated cholera vaccine position paper in 2010, the Gavi Alliance initiated stock-piling of oral cholera vaccines, and these have been effectively deployed in Haiti and Africa to respond to outbreaks. Supply was an issue, when there was only one pre-qualified manufacturer of the vaccine without the B subunit with a limited supply capacity, but recently Euvichol (made by Eubiotics, South Korea), a vaccine similar to Shanchol (made by Shantha Biotechnics, a subsidiary of Sanofi Pasteur), the first WHO pre-qualified killed oral bivalent cholera vaccine, has been pre-qualified by WHO. Other vaccines are also in development in India, by public sector undertakings such as BIBCOL, a company established by the Department of Biotechnology which now provides oral polio vaccine to the national immunization programme, and by Hilleman Laboratories, a company established in India through a partnership between the Wellcome Trust and the multinational vaccine manufacturer, Merck & Co.

2.4. The role of the NTAGI in decision-making on cholera vaccines

Determining public health priority is a complex process involving several stakeholders and requires insight into epidemiological, social, political and financial implications of the targeted disease. For vaccines, the NTAGI has been constituted as an independent advisory body to make recommendations to the MOHFW [6], and the technical sub-committee of NTAGI constitutes working groups to examine priorities and advise on next steps for vaccine preventable diseases. The cholera vaccine working group has made recommendations, which will be discussed by the NTAGI in conjunction with the ongoing revision of the WHO recommendations, and with appropriate stake holders before formal decisions or plans are made by the MOHFW.

Further, the vaccination strategy for delivery of vaccines will need to be considered. The current approach is to conduct mass vaccination campaigns involving all those over one year of age [8]. Per the new guidance from WHO, campaigns can be repeated every three years. Since cholera is a disease where other concomitant interventions are expected to decrease incidence or time, cholera disease burden needs to be continually reviewed to assess whether or further vaccination is needed. In areas with endemic disease, the government should consider which is the most appropriate and feasible vaccination strategy for specific areas or populations at risk, and how vaccination can best be delivered and monitored.

3. Conclusion

In summary, India has a robust mechanism for decision-making on policies for vaccine introduction, and this process has been initiated for oral cholera vaccines. The lack of strong reporting systems and surveillance is a key need that has to be addressed both in order to measure the burden and to evaluate the impact of vaccines and other interventions when introduced. Oral cholera vaccines are now available and affordable, and the government should consider how best to use this valuable tool in addition to complementary approaches for prevention of a major public health problem.

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References