

Why is the Oral Cholera Vaccine Underused in India?

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INTRODUCTION

Cholera is an acute intestinal infection caused by ingestion of food or water contaminated with the bacterium *Vibrio cholerae*. The disease is associated with poverty, lack of clean drinking water, inadequate sanitation and poor hygiene. *V. cholerae* has a short incubation period, ranging between a few hours to five days. It is characterised by explosive watery diarrhoea accompanied by vomiting, followed by rapid dehydration, and in the absence of prompt treatment, death can ensue within a matter of 3-4 hours. Treatments include administration of antibiotics and Oral Rehydration Solution (ORS). Although prompt administration of ORS is highly effective and strongly recommended by experts, its use is rather low. Globally, the usage rate of ORS is 75%, while in India this value is only 23-42%. The disease can exhibit endemic or epidemic patterns. The incidence of cholera has been steadily rising worldwide since 2005 and it is estimated that the annual burden of cholera is 1.3-4.0 million cases and 21,000-143,000 deaths worldwide [1].

PREVENTION OF CHOLERA

Cholera can be prevented by a two-pronged approach- (i) Water, Sanitation and Hygiene (WASH) and (ii) Vaccination.

WATER, SANITATION AND HYGIENE

Water, Sanitation and Hygiene (WASH) is a global programme implemented by the United Nations Children's Fund (UNICEF). All three components of the WASH strategy are grouped together because all three are interdependent on each other. For example, in the absence of toilets, water becomes contaminated and without clean water, hygiene is not possible. Therefore, all three WASH components complement, support and strengthen one another- if one is absent, the other two cannot progress [2].

The Sustainable Development Goal (SDG) 6, calls for clean water and sanitation for all people across the globe: "Ensure availability and sustainable management of water and sanitation for all". Globally, 2.6 billion people have gained access to improved water supplies since 1990, but 666 million people still lack access. In India, 1 in 5 (102,813) people die due to severe diarrhoea. Moreover, over 20% of the Indian population live in states which are not declared as 'open defecation free'. As per World Bank data for 2015-2016, more than 520 million Indians were defecating in the open, which is the highest in the world. However, it is encouraging to note that sanitation practices are slowly improving due to the implementation of several flagship programmes of the Government of India, such as the *Swachh Bharat Abhiyan*, the National Rural Drinking Water Programme, and the *Namami Gange Programme*, which aims to clean and conserve the river Ganga [3].

The 'WHO/UNICEF Joint Monitoring Programme (JMP) for Water Supply, Sanitation and Hygiene' has published its First Report entitled 'Progress on Drinking Water, Sanitation and Hygiene: 2017 Update and SDG Baselines' on 12th July 2017 [4]. As per this report,

the following statistics are available on the status of Drinking Water, Sanitation and Hygiene in 2015 with reference to India [5]:

Drinking water: The basic drinking water coverage was available for 91.04% of the population. There was limited improvement in case of 1.40% of the population, while there was no improvement in drinking water supply for 6.74% of the population. Alarming, 0.82% of the population still depended on surface water, such as rivers and ponds as sources of drinking water.

Sanitation: Approximately 54.35% of the population had access to basic sanitation facilities, while 11.88% of the population had limited improvement in access. For 2.67% of the population, there was no improvement in sanitary facilities, whereas a staggering 31.10% of the population still practiced open defecation.

Hygiene: Approximately 59.30% of the population had access to basic hygienic facilities such as soap and water for hand washing. There was limited improvement in access in case of 37.94% of the population, while 2.76% of the population did not have any access to hygienic facilities at all.

VACCINATION AGAINST CHOLERA

The immunity arising from cholera vaccine is not life-long. It lasts for about 3-5 years. Cholera vaccines can be deployed very easily and elicit a quick immune response, thus making them effective tools for public health interventions, both in endemic and epidemic situations. The concept of cholera as a vaccine preventable disease arose in the days of Robert Koch, who discovered the "comma" bacillus or *V. cholerae*. Since then, several injectable whole cell based cholera vaccines have been developed. These parenteral vaccines were administered by intramuscular (IM) and subcutaneous (SC) routes and conferred a protection of 30-50% for 3-5 months. However, these injectable cholera vaccines exhibited many side effects, such as pain, fever, erythema, headache, and malaise. As a result, these vaccines were discontinued by the World Health Organisation (WHO) in the early 1970s [6]. As a result, researchers subsequently directed their efforts towards developing Oral Cholera Vaccines (OCVs).

ORAL CHOLERA VACCINES

There are currently three WHO prequalified OCVs, namely, Dukoral®, Shanchol™, and Euvichol®. All three vaccines require two doses to confer full protection. These three major OCVs are discussed below:

Dukoral®: This vaccine is manufactured by SBL Vaccin AB, Stockholm, Sweden. It consists of killed whole cell *V. cholerae* O1 with purified recombinant B-subunit of cholera toxin (WC/rBS). This two-dose vaccine is administered in a buffer solution containing 150 mL of clean water. It can be given to all individuals above 2 years of age. There must be a minimum 7 days, and less than 6 weeks delay between the two doses. Children aged 2-5 years require a third (booster) dose. The protection starts roughly 1 week after ingestion of the last dose and confers 85-90% protection at 6 months in all age

groups, and 62% protection at 1 year in case of adults. This vaccine is mainly recommended for travellers and has been licensed in over 60 countries worldwide [1]. Dukoral® is safe for pregnant women as it is not absorbed into the bloodstream, but remains in the gut. The cost of this vaccine is USD 4.7-9.4 per dose [7].

Shanchol™: This vaccine is manufactured by Shantha Biotechnics, which is a Sanofi Company based in Hyderabad, India. The vaccine was WHO prequalified way back in 2011 and has since been licensed in India, Bangladesh and 16 other countries in South America, Africa and Asia. It is a two-dose, bivalent vaccine that protects against both *V. cholerae* O1 and O139. Unlike Dukoral®, this vaccine does not contain the bacterial toxin B-subunit and thus does not require any buffer for administration. The two doses are administered 2 weeks apart. It confers 67% protection in all age groups who received two doses of the vaccine. Shanchol™ is recommended for all individuals above 1 years of age and the duration of protection is up to 3 years. This vaccine is recommended for mass vaccination. It costs USD 1.85 per dose [7].

Euvichol®: This vaccine is manufactured by Eubiologics, Seoul, South Korea. Like Shanchol™, this vaccine does not contain the bacterial toxin B-subunit and thus does not require any buffer for administration. This two-dose vaccine can be administered to all individuals above 1 year of age. There must be a gap of 2 weeks between the two doses. The vaccine confers 66-67% protection for up to 3 years following administration of both doses, but provides short-term protection with one dose. This vaccine is recommended for mass vaccination campaigns, especially during cholera outbreaks [1].

Shanchol™ and Euvichol® are both available for mass vaccination through the Global OCV Stockpile, which is supported by Gavi, the Vaccine Alliance. Importantly, over 20 million doses of OCVs have been used in mass vaccination campaigns so far.

Vaxchora®: An Oral Cholera Vaccine Licensed for Use in USA

Besides the above three OCVs, the United States Food and Drug Administration (USFDA) has approved a single-dose OCV called Vaxchora® (lyophilised CVD 103-HgR) for use in USA. The Advisory Committee on Immunisation Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in Atlanta, approved the vaccine for use in adults aged between 18-64 years travelling to areas of the globe where there is active cholera transmission. However, this vaccine is very costly (USD 250) and therefore, is unsuitable for mass vaccination campaigns [8].

REASONS FOR UNDERUSE OF ORAL CHOLERA VACCINES IN INDIA

Epidemics of cholera continue to be a common occurrence among marginalised poor populations in remote areas. It is quite surprising that in India, where cholera exists in sporadic, endemic and epidemic forms, and despite the availability of a highly efficacious and safe OCV, it continues to be underused in public health vaccination programmes. The possible reasons for the underuse of OCV have been analysed [9].

Lack of awareness: The introduction of a vaccine in the public health system heavily relies on the demand from its potential users. The underlying reason for the paucity of demand for OCV is a lack of awareness and ignorance about the disease, as well as a poor understanding of potential preventive measures among the affected communities. On average, a family of five residing in cholera endemic areas earns a meagre INR 4,280 per month. Thus, abject poverty coupled with the heavy burden of diarrhoeal diseases such as cholera creates a vicious cycle from which there is no respite. Moreover, the out-of-pocket expenses are also astronomical, with over 75% of healthcare expenses having to be borne by patients

and their families. This further exacerbates the deprivation, with over 39 million additional Indians falling into poverty every year due to the rising health expenditure. As a result, those who are aware of the existence of OCV are ready to receive it only if it is provided free-of-charge.

Under reporting: Cholera is grossly under reported in India. The data on the incidence of cholera in India is gathered by the Integrated Disease Surveillance Programme (IDSP), which is a Government of India initiative. The data obtained from various states is compiled by the IDSP to generate national level data. One of the major reasons for underreporting of cholera cases by clinicians is the non-availability of point-of-care rapid diagnostic tests (RDTs) for cholera.

As a result most of the cholera cases get reported as 'acute diarrhoeal disease'. Moreover, inconsistencies in case definition also add to the problem. Unfortunately, since these under reported datasets are being utilised by the decision makers and policymakers, they are under the impression that cholera does not exist in the country. Therefore, there is an urgent need to obtain accurate data that gives a realistic picture of the burden of cholera in India.

Misperception: There is a misperception about cholera among physicians in India largely arising from consistent under reporting. Physicians practising in metropolitan areas rarely come across cholera cases as most of the patients are well-to-do and therefore, have access to adequate clean drinking water and sanitation facilities. Moreover, most acute diarrhoeal cases are treated at primary health centres (PHCs), rather than being treated by private medical practitioners. This is especially true in rural areas. Hence, there is a need for concerted efforts to inform practicing physicians about the epidemiology of cholera, its persistence in sub-geographic regions and capability of rapidly spreading to hitherto unaffected parts of the country.

Ambiguous case definition: The classical case definition for cholera requires that 'rice water stool' should be present in order to make a positive diagnosis. However, this is observed only in severe cholera (*cholera gravis*), whereas in most mild infections, loose or watery stool is present that cannot be distinguished from other causes of diarrhoea. Moreover, the stool may be absolutely normal in most cases of asymptomatic infections. As per the National Health Profile 2018 [10], between January and December 2017, there were 12,927,212 cases and 1,331 deaths arising from acute diarrhoeal diseases, of which there were only 474 cholera cases and 3 deaths. This clearly indicates that the number of cholera cases is miniscule in comparison to the number of cases due to acute diarrhoeal diseases. This leads to gross under reporting of cholera cases due to a faulty case definition for the disease.

Political and socio-economic factors: Cholera outbreaks are intrinsically associated with a lack of access to clean drinking water and proper sanitation facilities. Since this is the responsibility of the state, it creates a bad impression on the state health services in the public eye. As a result, there is often a tendency by politicians to brush these occurrences under the carpet. Importantly, gross underestimation of cholera cases could also be attributed to other socio-economic factors, including the stigma attached to the disease in Indian society, which could lead to economic deprivation for certain communities.

Demand and supply gap: It is essential that the OCV should be readily available so that its supply is adequate in order for it to be introduced in the public health programme. There are three essential steps that should be followed in order to provide impetus for vaccine manufacture. These include (i) assessment of demand for the OCV in India, (ii) assessment of how much new vaccine manufacturers are willing to invest for manufacturing the OCV in developing countries like India, and (iii) having in place, the adequate incentives for new vaccine manufacturers so that any type of financial risk that may arise can be tackled. For example,

the demand for Shanchol™ in India is lacking, which has resulted in vaccine companies losing interest in the business venture in India. Moreover, depending on only one vaccine supplier for running a national vaccination programme poses a significant risk that could jeopardise the entire programme.

GLOBAL INITIATIVES FOR TACKLING CHOLERA

There are several global initiatives for tackling cholera, both nationally and internationally. Some of these are highlighted below:

IDEA: The Initiative against Diarrhoeal and Enteric diseases in Asia (IDEA) is based in Lyon, France. IDEA holds a meeting every alternate year in various countries in Asia, where experts from eight cholera-endemic Asian countries gather to deliberate and discuss about formulation of strategies to take forward the cholera agenda at the global and regional levels [11].

CCPC: The Coalition for Cholera Prevention and Control (CCPC) is an initiative that began in 2011 with funding from the Bill & Melinda Gates Foundation (BMGF). The CCPC has formulated a comprehensive integrated strategy for cholera prevention and control. This strategic framework identifies outdated recommendations and gaps in knowledge and formulates new recommendations and guidelines that target policymakers, policy implementers, donors, physicians, and researchers to tackle cholera through mass vaccination campaigns [12].

SAGE: The WHO Strategic Advisory Group of Experts (SAGE) on immunisation was established in 1999. The cholera experts of SAGE are responsible for analysing the results of Monitoring and Evaluation (M&E) activities implemented during OCV campaigns. It particularly focuses on vaccine safety, efficacy, acceptability, as well as the impact of vaccination on cholera transmission in endemic and epidemic settings. It also provides recommendations to WHO for formulating appropriate vaccination policies [13].

Stop Cholera: This initiative is also known as the DOVE (Delivering Oral Vaccine Effectively) Programme, which is spearheaded by Johns Hopkins Bloomberg School of Public Health. It includes experts from several organizations, including the BMGF, African Cholera Surveillance Network (AfriCHOL), International Vaccine Institute (IVI), UNICEF, and the International Federation of Red Cross and Red Crescent Societies (IFRC), among others. This multinational initiative has developed several important resources in the area of cholera prevention and control. It recommends that the OCV should be an integral component of comprehensive cholera

control strategies [14].

CONCLUSION

The prospect of eliminating cholera may soon become a reality. In October 2017, the Global Task Force on Cholera Control launched a strategy for controlling and eventually eliminating cholera. This programme is called '*Ending Cholera: A Roadmap to 2030*', which aims to reduce cholera deaths by 90% and to eliminate cholera in at least 20 countries worldwide by 2030.

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