A Policy Brief

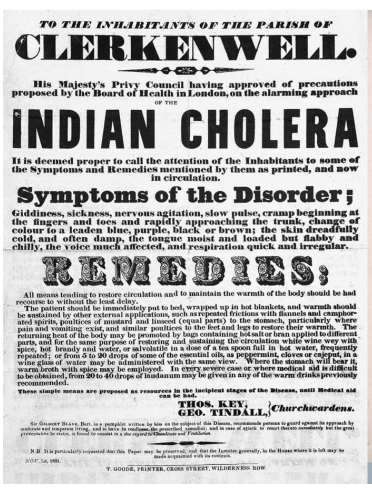
Oral Cholera Vaccines—worth a shot?

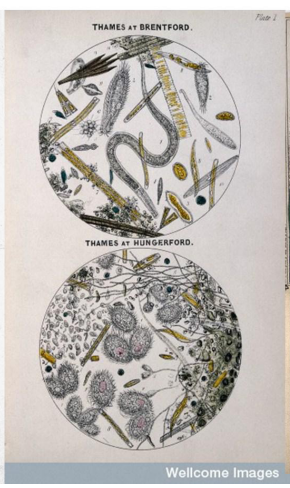
November 2017

Authors

Samiran Panda, Pranab Chatterjee, Alok K Deb, Suman Kanungo and Shanta Dutta

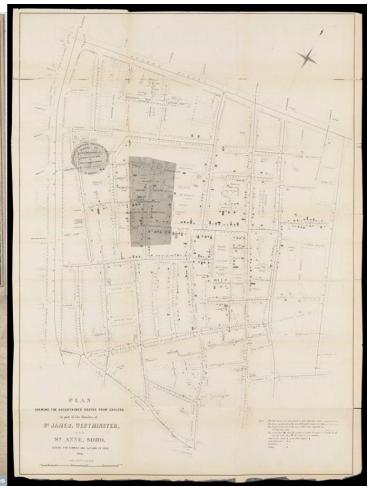
Indian Council of Medical Research (ICMR)


TO THE INHABITANTS OF THE PARISH OF
CLERKENWELL.
His Majesty's Privy Council having approved of precautions proposed by the Board of Health in London, on the alarming approach OF THE
INDIAN CHOLERA
It is deemed proper to call the attention of the Inhabitants to some of the Symptoms and Remedies mentioned by them as printed, and now in circulation.
Symptoms of the Disorder;
Giddiness, sickness, nervous agitation, slow pulse, cramp beginning at the fingers and toes and rapidly approaching the trunk, change of colour to a leaden blue, purple, black or brown; the skin dreadfully cold, and often damp, the tongue moist and loaded but flabby and chilly, the voice much affected, and respiration quick and irregular.
REMEDIES;
All means tending to restore circulation and to maintain the warmth of the body should be had recourse to without the least delay.
The patient should be immediately put to bed, wrapped up in hot blankets, and warmth should be sustained by other external applications, such as repeated frictions with flannels and camphorated spirits, poultices of mustard and linseed (equal parts) to the stomach, particularly where pain and vomiting exist, and similar poultices to the feet and legs to restore their warmth. The returning heat of the body may be promoted by bags containing hot salt or bran applied to different parts, and for the same purpose of restoring and sustaining the circulation white wine wey with spice, hot brandy and water, or salvolatile in a dose of a tea spoon full in hot water, frequently repeated; or from 5 to 20 drops of some of the essential oils, as peppermint, cloves or cayeput, in a wine glass of water may be administered with the same view. Where the stomach will bear it, warm broth with spice may be employed. In every severe case or where medical aid is difficult to be obtained, from 20 to 40 drops of laudanum may be given in any of the warm drinks previously recommended.
These simple means are proposed as resources in the incipient stages of the Disease, until Medical aid can be had.
THOS. KEY, GEO. TINDALL, } Churchwardens.
N.B. It is particularly requested that this Paper may be preserved, and that the Inmates generally, in the House where it is left may be made acquainted with its contents.
T. GOODE, PRINTER, CROSS STREET, WILDERNESS ROW.



Wellcome Images

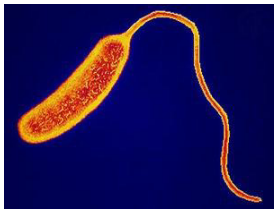
Wellcome Images



EXECUTIVE SUMMARY

The last two decades were exciting times in the history of development of oral cholera vaccines (OCVs). Field trials, demonstrating their protective efficacy, have witnessed participation from around the globe, such as India, Bangladesh, Mozambique, Zanzibar, Indonesia, and Vietnam.[1] A bivalent killed whole-cell OCV, proven safe and efficacious through a cluster randomized trial in an Indian city, has received in-country licensure.[2] The moot point now, therefore, is 'to use or not to use' the OCV at scale in India. A decision favouring 'use' would have major cost implications if the entire population of the country is to be covered.

The present narrative, through a systematic review, addresses the aforementioned policy conundrum. Our synthesis highlights that contrary to popular belief, cholera has its foothold firmly rooted in India. Frequently encountered symptoms of the disease are vomiting and at times, mild fever along with diarrhoea and faecal loss of salt and water leading to dehydration. Every year several outbreaks of the disease are reported from across the country. A few districts, based on the data from 'Integrated Disease Surveillance Program' (IDSP) (2011-2015), can even be labelled as endemic for cholera. However, we underline that the burden of cholera estimated for India is hamstrung by lack of robust surveillance as well as scarcity of incidence studies. Analysis of outbreak reports indicates that some settlements and populations are more vulnerable to diarrhoea and cholera compared to others. This heterogeneity provides an opportunity to prioritize areas for intervention but also cautions against applying incidence data obtained from one study from Kolkata to all of India. The short lasting nature of most of the recent cholera out-breaks in India (2-3 weeks), requirement of two doses of the licensed OCV to be administered with a gap of 2 weeks in between and emerging evidence that considerable efficacy could be attained by single dose administration of the same vaccine call for pragmatic approaches. We recommend that a) existing surveillance system for cholera be strengthened, b) mapping of vulnerability to cholera as pertinent to population groups and geographical locations be continued and existing information be used for decision making, c) single dose bivalent killed OCV (licensed in India) be deployed in operational exploration mode in selected settings and in pre-cholera season and d) investment for safe water and sanitation as well as hygienic practices be boosted. The cost of inaction today could mean lives claimed by cholera in underserved areas, deepening of poverty and inequity, and perpetuation of expenses needed to tackle recurrent outbreaks of cholera and other diarrheal diseases tomorrow.



BACKGROUND

History of cholera in India dates back to ancient times. However, recorded accounts of the disease marks 1817 as the year of devastation for the country, which is also considered to be the year of commencement of the first pandemic of cholera.[3] The basic and clinical research in and outside India have made significant contributions to the understanding of the disease pathology, transmission dynamics and improvement in management approaches. Worth noting is that the Indian Council of Medical Research (ICMR) supported some of these endeavours starting in the early 1950s. For example, the pioneering work with rabbit ileal loop,[4,5] providing convincing proof of the presence of toxin in bacteria-free culture-filtrate of *V. cholera,* the causative organism of cholera, was supported by a grant from ICMR. While mortality due to cholera in India has considerably reduced over time due to gradually increasing use of oral rehydration salt solution, the morbidity yet remains a matter of concern. Currently the country is passing through the 7th pandemic, the wave of which started in 1961 in Indonesia and spread rapidly to other countries in Asia, Europe and Africa. In 1991 the wave made in-roads in Latin America, which had been free of cholera for more than a century.

CONTEXT

Developments around OCVs globally over the last two decades have been exciting. It is worth noting that a bivalent killed whole-cell oral cholera vaccine, proven safe and efficacious through a cluster randomized trial in an Indian city, has received in-country licensure for which the trial results played a pivotal role. In this context we conducted a systematic review to explore opportunities and policy options pertinent to use of OCV in India.

AIM OF THE PRESENT POLICY BRIEF

To inform evidence based policy and program discussion on the use of OCV in India

OBJECTIVES

To synthesize evidences for mapping of vulnerability of people to cholera in India
To examine appropriateness of administration of licensed OCV at scale

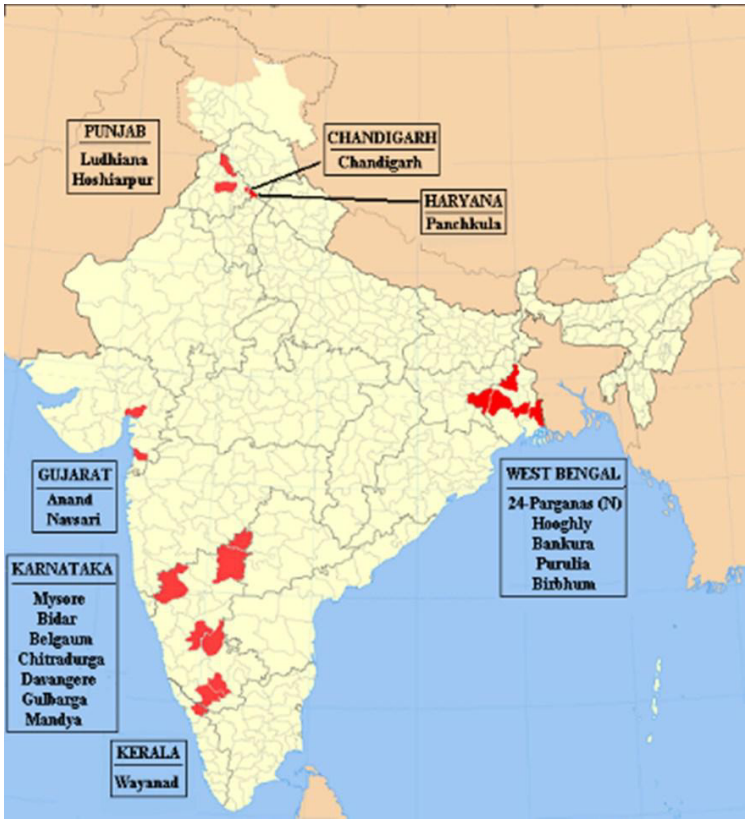
GAP ANALYSIS

We grouped the gaps, identified through a systematic review, in three categories; i) hurdles in the path of estimating burden of cholera in India, ii) delineation of vulnerability of population groups and iii) absence of analytical discourse on policy and program perspectives of administration of two doses of bivalent killed whole cell OCV.

First, the data generated on countrywide cholera case load by using IDSP-information suffers from underreporting. It is estimated that the actual cases could be at least six times higher than what is reported.[6] Subsequent attempts to refine the estimates have however extrapolated annual incidence data obtained from a single population-based surveillance site located in impoverished urban slums of Kolkata to the estimated 'population-at-risk of cholera' for the whole country - an approach which has its inherent limitations.

Second, no countrywide monitoring mechanism to map the vulnerability of population groups to cholera is currently operational. However, analysis of outbreak reports published in peer reviewed journals in conjunction with the IDSP generated information help highlight that certain districts and population groups are at higher risk of cholera compared to others. For example, residents of labour settlements, urban slum dwellers, workers in tea gardens, vagrants in shelter homes, and colonies inhabited by marginalized sections of the society bore most of the brunt.

Third, the two doses of the OCV, which has been licensed for use in India, needs to be administered with a gap of 2 weeks in between. This, and other logistic requirements, such as maintenance of cold chain, and mobilizing large human resources to manage vaccination booths if the entire population of an administrative unit (district or block) is to be covered, poses hurdles on the way of deployment of this vaccine on a large scale. A detailed account of these challenges can be obtained from the Odisha experience where the public health system was engaged on a pilot basis to vaccinate a target population of 51,488 in Satyabadi block of Puri district.[7]



The map shows 19 of the 685 Indian districts, which can be termed endemic for cholera based on the confirmed cases reported for 3 or more years during a five year span (2011-2015). Seventeen of these endemic districts and 34 other non-endemic districts reported multiple events of cholera (two or more) in a year during the same five year period. Altogether 53 such districts can therefore be prioritized for prevention intervention.

Analysis of recent in-country outbreak reports is worth noting in this context. Occurrences of cholera during these seasonal outbreaks (May-July) always dwindled down in 2-3 weeks time. The logistic advantages of a single-dose OCV based approach needs to be weighed against these challenges as well as efficacy data and experiences from real world settings.[8-10]

Economic as well as equity considerations highlight the advantage of using OCV in India. While in-patient treatment cost for each case of cholera amounts to approximately US$ 41, the two doses of OCV can be administered at about one-tenth the cost and a single-dose administration would cost even less (US$1.85 per dose and delivery cost of US$ 0.49 per dose). The perpetual costs of managing outbreaks every year and even multiple outbreaks in a year in certain vulnerable populations residing in high priority districts may be offset by such pre-emptive single-dose based OCV administration. On the other hand, not reaching out to the poor and vulnerable with an available low cost efficacious prevention tool would tantamount to 'public health neglect'.

POLICY RECOMMENDATIONS

a) Strengthen the existing surveillance system for cholera and other diarrheal diseases in the country

b) Continue mapping of vulnerability to cholera and other diarrheal diseases pertaining to population groups and geographical locations and concurrently use available data for decision making

c) Deploy single-dose bivalent killed OCV (licensed in India) in operational exploration mode in high priority settings

d) Invest in improvement of safe water and sanitation through structural intervention and hygienic practices through innovative behaviour change communication

The understanding that health policies often need to be formulated in an environment of inadequate empirical evidence,[11] and require periodic review as more answers to public health questions emerge, forms the cornerstone of the current policy brief. In line with the recent WHO position paper on OCVs,[12] and in light of the Odisha experience, we highlight that the prevailing situation in India does not merit coverage of an entire birth cohort with OCVs. Rather, the strategies should focus on vulnerable groups and settings. Vaccination strategies which target the most vulnerable sections of the society should be endorsed; children between 1-15 years belong to such category and could be reached through *anganwadi* centres under integrated child development scheme and schools in both formal and informal settings. Programmatic deployment of OCVs should go hand in hand with infrastructure and systems strengthening to ensure appropriate Water, Sanitation and Hygiene (WaSH) services, improved surveillance, and advocacy, communication and social mobilization (ACSM) for engaging community to mitigate the risk of cholera. Finally, once a decision is made about deployment, OCV administration in India would be able to draw upon in-country as well as global experiences around ensuring stockpiles and maintenance of supply in the field, with other logistic requirements, such as cold chain.

KEY REFERENCES

1. Clemens J and Holmgren J. When, how, and where can oral cholera vaccines be used to interrupt cholera outbreaks? Current Topics in Microbiology and Immunology 2014; 379: 231-258. doi:10.1007/82_2013_353.
2. Bhattacharya SK, Sur D, Ali M, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a clus-ter-randomized double-blind, placebo-controlled trial. *Lancet Infectious Disease* 2013; 13:1050-1056. doi:10.1016/s1473-3099(13) 70273-1.
3. Polllitzer R. Cholera; *World Health Organization Monograph Series* No 43. WHO (Geneva) 1959.
4. De SN, Chatterje DN. An experimental study of the mechanism of action of Vibriod cholerae on the intestinal mucous membrane. *Journal of Pathology and Bacteriology* 1953;66:559–62.
5. De SN. Enterotoxicity of bacteria-free culture-filtrate of Vibrio cholerae. *Nature* 1959;183:1533–4.
6. Kanungo S, Sah BK, Lopez AL, et al. Cholera in India: An analysis of reports, 1997-2006. *Bulletin of World Health Organization* 2010;88:185–191. doi:10.2471/BLT.09.073460.
7. Kar SK, et al. Mass Vaccination with a New, Less Expensive Oral Cholera Vaccine Using Public Health Infrastructure in India: The Odisha Model. *PLoS Neglected Tropical Diseases* 2014;8:e2629. doi:10.1371/journal.pntd.0002629.
8. Qadri F, Wierzba TF, Ali M, Chowdhury F, Khan AI, Saha A, et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *New England Journal of Medicine* 2016;374:1723–32. doi:10.1056/NEJMoa1510330.
9. Azman AS, Parker LA, Rumunu J, Tadesse F, Grandesso F, Deng LL, et al. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. *Lancet Global Health* 2016;4:e856–63. doi:10.1016/S2214-109X(16)30211-X.
10. Azman AS, Luquero FJ, Ciglenecki I, Grais RF, Sack DA, Lessler J. The Impact of a One-Dose versus Two-Dose Oral Cholera Vaccine Regimen in Outbreak Settings: A Modeling Study. *PLoS Medicine* 2015;12:e1001867. doi:10.1371/journal.pmed.1001867.
11. Anderson LM, Brownson RC, Fullilove MT, Teutsch SM, Novick LF, Fielding J et al. Evidence-Based Public Health Policy and Practice: Promises and Limits. Am J Prev Med 2005; 28: 226–230.
12. World Health Organization (WHO). Cholera vaccines: who position paper – August 2017. Weekly Epidemiological Record, no 34, 25 August 2017.

ACKNOWLEDGEMENTS

Inputs obtained from Professor Kanchan Mukherjee, Chairperson, Centre for Health Policy, Planning and Management, School of Health Systems Studies, Tata Institute of Social Sciences, Mumbai and Dr. Suchita Bhattacharya, Freelance Consultant and Visiting Fellow at the University of Liverpool, UK, ICMR Workshop on 'Writing Policy Brief' in July 2017 are sincerely acknowledged. Dr. Soumya Swaminathan, Director General, ICMR and Secretary, Department of Health Research (DHR), Ministry of Health & Family Welfare (MoHFW), Government of India, Dr. S. Mehendale, Additional Director General, ICMR, Dr. Rajni Kant Srivastava, Scientist F, Head Research Management, Policy Planning & Coordination Division, ICMR, and Dr Gagandeep Kang, Executive Director, Translational Health Science and Technology Institute, Department of Biotechnology, Government of India are also acknowledged for their critical reading and commenting on the draft of this policy brief.