1 Introducing Cholera Vaccination in Asia, Africa and Haiti: a Meeting Report

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9 **Keywords**

10 Cholera; Cholera vaccination; Oral vaccine; Vaccine demonstration; Vaccine stockpile; Acceptability;

11 Feasibility

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INTRODUCTION

Orally-administered cholera vaccine (OCV) has been increasingly assessed as an additional tool to intervene against endemic and epidemic cholera. In 2013, short- and long-term field experience with OCV under nine distinctive field settings was reported from India, Bangladesh, Vietnam, Guinea, Haiti, and Thailand. Lead investigators from each of these projects presented their findings at a symposium chaired by Drs. David A. Sack and Robert H. Hall at the Vaccines for Enteric Diseases (VED) Conference in Bangkok on November 7, 2013. The objective of the symposium was to describe the unique features of each setting and project, share field experience of implementing cholera vaccination, discuss results, and identify constraints to the wider use of OCV. The VED provided a forum where >200 attendees engaged with this exciting and potentially decisive new development in the cholera field.

The three presently licensed cholera vaccines are formulations of killed whole bacterial cells for oral administration. Two of these vaccines are pre-qualified (PQ) by the World Health Organization (WHO) allowing for purchase by agencies of the United Nations: Dukoral® (PQ 2001) and Shanchol® (PQ 2011). Shanchol®, a lower cost vaccine consisting of 1.5 ml per dose and not requiring a buffer, was selected for the recently created global stockpile of OCV.[1] Dukoral®, which includes cholera toxin B subunit and is more costly, comprises two doses each of 3 ml vaccine in 150 ml of NaHCO₃ buffer to preserve the B subunit. The third OCV formulation (mORCVax®), similar to Shanchol®, is licensed, produced, and exclusively used in Vietnam, but is not WHO PQ. The vaccines used in the projects described below are listed in Table 1.

Dr. David Sack opened the symposium by acknowledging the many major contributors to the long-running effort to introduce cholera vaccines. Dr. Sack noted that the currently licensed killed OCVs were

developed in the early 1980s, and it has taken many years for them to reach this nascent stage of international implementation. By contrast, the national program in Vietnam has vaccinated over 10 million persons since 1998. Turning points for OCV came when WHO revised its position in 2010[2] to recommend the use of vaccine both in areas endemic for cholera or at risk of outbreaks, and in 2011 when Shanchol® received WHO PQ.[3] Supporting these developments was the resolution by the World Health Assembly in 2011 supporting the use of OCV as part of an integrated cholera strategy.[4] These important developments brought OCV to the attention of a broader community of public health officials and implementation agencies.

Recent progress has been dramatic. By the end of 2013, it was estimated that about 1.2 million doses of Shanchol™ had been administered in vaccination campaigns in Asia, Africa and the Caribbean[5]. Major UN and international non-governmental health organizations (NGOs) became unified in active support for OCV use, and WHO established a stockpile of 2 million doses of Shanchol™. In November 2013, the Board of the Global Alliance for Vaccines and Immunization (GAVI) approved a contribution towards the cost of expanding the stockpile, and endorsed a net budget increase to facilitate increasing the stockpile to 20M doses of OCV for 2014-8.[6]

At this early stage of OCV introduction, it is important to document and disseminate knowledge gained from field experience to allay concerns about safety, effectiveness, acceptability, resource allocation, cost; and the overall practicality of implementing sufficiently timely and large campaigns to have an impact. The second need is to collect and analyze information on the duration of protection, use in pregnancy, thermostability, herd protection, and single dose effectiveness under field conditions. The results of such analyses could radically influence the acceptability, feasibility, and efficiency of cholera

control campaigns when large outbreaks and humanitarian crises are confronted by inadequate funds, stretched human resources, and finite supplies of vaccine.

FINDINGS FROM SEVEN RECENT CAMPAIGNS USING ORAL CHOLERA VACCINE

The symposium reported highly encouraging progress from seven groups that had recently implemented OCV programs in eleven settings (Table 2). The presentations came from a variety of agencies, in different geographic areas, and with different indications for initiating OCV programs[7-28]. Projects ranged from research protocols with informed consent under regulatory oversight to programs under the national EPI. Quantitative and qualitative data from the Caribbean, across Africa, South Asia, and to the South China Sea coast of Vietnam have allayed most of the previously-expressed concerns of government and NGOs. Vaccination with OCV was demonstrably safe, acceptable, effective and feasible in all epidemic and endemic settings where these parameters were measured. Only minor adverse events have been associated with OCV from over 10m doses administered in the >13 year program in Vietnam, and 1.6 million doses administered in recent projects. High short-term effectiveness was found in Guinea[24], 5-year effectiveness was documented in Kolkata, India, [10] and long-term disease control and environmental decontamination observed in Vietnam[21].

Vaccination, knowledge, attitude, and practices programs (KAP); and water, sanitation, and hygiene interventions (WaSH) were demonstrably integrated and mutually supportive in Mae La, Thailand, and in Haiti; helping to pave the way for strengthening public health programs. Direct evidence from Vietnam and Bangladesh showed that OCV is readily integrated into national vaccination programs, and other projects predicted similar efficiencies of integration.

The constraints reported had much in common across sites: consensus building among stakeholders was a significant challenge; but essential and manageable. And enthusiasm is now high for further implementation of OCV across the cholera map. Investigators anticipated that constraints will be lessened when the stakeholder community gains more appreciation of recent and future demonstration projects. Clearly a vaccine giving protection from the first dose, especially in infants, is also a desirable long-term aspiration. Some additional limitations of OCV were evident, especially in the most difficult settings; the cold chain requirement, pregnancy exclusion, and single-dose vialing pre-eminent among them. Interestingly, in Guinea, vaccines were transported and used at ambient temperature on vaccination day[22]. Vaccines left over at the end of vaccination day were returned to the cold chain and used first on the following day. Before administration, the vaccine vial monitor (VVM) was checked for stability; the vial was shaken, opened, and administered or self-administered under observation. All VVM remained valid during the campaign.

THE CHOLERA VACCINE STOCKPILE

Dr. Stephen Martin presented information on the OCV stockpile. In April of 2012, a technical working group of cholera experts convened and mandated WHO and partners to create a global stockpile of OCV to help control cholera epidemics. From July 2013 until June 2014, the stockpile will acquire tranches of vaccine amounting to 2 million doses of WHO-prequalified Shanchol®, and will make them available through the International Coordinating Group (ICG). The management, distribution, and evaluation of a rotating OCV stockpile is modeled on existing meningococcal meningitis and yellow fever (YF) vaccine stockpiles.

In 1996, Africa experienced the largest recorded outbreak of epidemic meningitis in history, with more than 200,000 cases and 20,000 deaths. The emergency response fully exhausted international vaccine reserves. A vaccine stockpile was mandated, and an ICG established in 1997 with four decision-making partners: the International Federation of Red Cross and Red Crescent Societies (IFRC), MSF, United Nations Children's Fund (UNICEF), and WHO; which also provided the Secretariat. The ICG subsequently adopted the rotating YF vaccine stockpile of ~12 million doses when it was established in 2004. Each epidemic season the ICG receives and assesses from 10 to 35 vaccine requests. In total, over 50 million doses of meningococcal vaccine and 90 million doses of YF vaccine have been released to date.

For the OCV stockpile the ICG considers three potential scenarios for the deployment of vaccine: outbreaks, humanitarian emergencies, and high risk settings. As with the process for accessing meningococcal meningitis and YF vaccines, the process for accessing the OCV stockpile will involve submission and circulation of a request to the ICG Secretariat, followed within 48h by the ICG decision. Where approved, procurement, packing, shipment, and country receipt, will take a maximum of 10 days. Reimbursement of vaccine cost within 60 days is requested to sustain the stockpile.

The April 2012 mandate regarding OCV included the following statement: "A system of short- and longer-term monitoring and evaluation should be embedded within the OCV stockpile mechanism". As experience and data accrue, a rigorous and iterative system of monitoring and evaluation (M&E) will facilitate continuous improvement in the structure, function, and field effectiveness of the stockpile. In addition, experience in a range of settings should enable the contributions of vaccine and other interventions to be assessed and optimized. The M&E Working Group has identified key process and outcome indicators that are necessary for M&E, and has developed a framework of activities, standard protocols, and technical support to acquire these data and report to the ICG. Further details of the

WHO Oral Cholera Vaccine Stockpile program including contacts, organization, and the request form with guidance for planning and use are publically available.

The first challenge for the ICG membership is to improve awareness and understanding of this important new public health tool. The necessary processes must be conveyed, especially in generating M&E data. WHO launched a series of instructional workshops on the OCV stockpile at the Harmonization for Health in Africa (HHA) meeting in Dakar, Senegal (in July 2013), followed by a regional meeting at EMRO (October 2013) with South Sudan, Sudan, Afghanistan, Pakistan, Iran, Iraq, and Djibouti. The long term objective is to integrate the OCV stockpile into a more comprehensive, effective and sustainable response to cholera.

The next step in developing and deploying the OCV stockpile was taken at the November 20th 2013 Board meeting of the Global Alliance for Vaccines and Immunization (GAVI), when the stockpile mechanism was endorsed and the expansion of global OCV production capacity encouraged. Implicit in the GAVI process of providing a commitment is the need for robust M&E of Shanchol® in the field. Analysis of impact and cost-effectiveness will inform larger decisions in the future.

SUMMARY OUTCOME

The summary outcome has been to answer concerns about OCV with direct field experience; to correct misconceptions, improve understanding, and identify significant limitations to broader implementation. Many previously-identified constraints were successfully overcome during planning and implementation of the studies described above. The presenters uniformly reported that vaccination with OCV is demonstrably safe, feasible, acceptable, and both compatible and non-competitive with other cholera control activities such as KAP and WaSH. The present constraints are now less subjective: a large and

sustainable vaccine supply, in-depth communication with the key constituencies, and effective implementation in cholera-afflicted countries. Several more fundamental limitations in vaccine performance may be resolved by improved formulations and candidate vaccines now in an advanced stage of development. Although the aggregate number of vaccinations is still a small proportion of those needed and the effectiveness of the latest campaigns still remains to be determined, this may be the historical turning point when prevention by vaccination finally and decisively began to impact cholera in the field.

The remaining challenges include improving field- and cost-effectiveness through iterative monitoring and evaluation. This will require improved tools and methods for surveillance and reporting so that vaccine effectiveness can be estimated in remote areas where cholera most commonly occurs, and in different populations, different settings, and under different dosing regimens. And despite dramatic recent progress, the efforts to date (outside Vietnam) are still relatively small and exploratory: scaling up the entire enterprise to match the global scale of cholera is the greatest challenge and opportunity.

CONCLUSION

The symposium concluded that the year 2013 may mark one of the few decisive years in the centuries-long effort against cholera. There has been a dramatic advance in the understanding and appreciation of OCV as a public health tool. The success that has been achieved is attributable to the effort, dedication and collaboration of a great many persons, organizations and donors over years and decades. But the community as a whole looks forward to the future with substantially reinforced expertise, resources, consensus, and a new-found sense of optimism.

Acknowledgements

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264 **Table 1:**
265 **The components of currently available Killed Orally-Administered Cholera Vaccines.**
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Trade Name, Manufacturer, & License	Components	Biotype, Serogroup, Serotype
Dukoral® SBL Vaccin AB (Sweden) Licensed (1991) PQ (2001) Recombinant cholera toxin B subunit (rCTB) 1 mg (from <i>V. cholerae</i> O1 Inaba, classical biotype strain 213.) Orally administered as 3ml in 150 ml NaHCO ₃ per dose	31.25x10 ⁹ cells <i>V. cholerae</i> (heat inactivated)	Classical O1 Inaba
	31.25x10 ⁹ cells <i>V. cholerae</i> (formalin inactivated)	El Tor O1 Inaba
	31.25x10 ⁹ cells <i>V. cholerae</i> (heat inactivated)	Classical O1 Ogawa
	31.25x10 ⁹ cells <i>V. cholerae</i> (formalin inactivated)	Classical O1 Ogawa
ORC-Vax, NIHE, Hanoi, Vietnam Formulation 1: Licensed in Vietnam (1997)	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> Phil 6973 formalin killed	El Tor O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> Cairo 50 heat killed	Classical O1 Ogawa
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> classical 569B formalin killed	Classical O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> classical Cairo 48 heat killed	Classical O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam Formulation 2: Licensed in Vietnam (1997)	5.0 x 10 ¹⁰ cells <i>V. cholerae</i> Phil 6973 formalin killed	El Tor O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> Cairo 50 heat killed	Classical O1 Ogawa
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> classical 569B formalin killed	Classical O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> classical Cairo 48 heat killed	Classical O1 Inaba
	5.0 x 10 ¹⁰ cells <i>V. cholerae</i> 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam Formulation 3: Licensed in Vietnam (2000)	5.0 x 10 ¹⁰ cells <i>V. cholerae</i> Phil 6973 formalin killed	El Tor O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> Cairo 50 heat killed	Classical O1 Ogawa
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> classical 569B formalin killed	Classical O1 Inaba
	2.5 x 10 ¹⁰ cells <i>V. cholerae</i> 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam Formulation 4: Licensed in Vietnam (2009)	600 EU LPS* <i>V. cholerae</i> Phil 6973 formalin killed	El Tor O1 Inaba
	300 EU LPS <i>V. cholerae</i> Cairo 50 heat killed	Classical O1 Ogawa
	300 EU LPS cells <i>V. cholerae</i> classical Cairo 48 heat killed	Classical O1 Inaba
	600 EU_LPS <i>V. cholerae</i> 4260B formalin killed	O139

Shanchol® Licensed in India (2009) PQ (2011) Orally administered as 1.5ml suspension per dose	600 EU LPS <i>V. cholerae</i> Phil 6973 formaldehyde killed	El Tor O1 Inaba
	300 EU LPS <i>V. cholerae</i> Cairo 50 heat killed	Classical O1 Ogawa
	300 EU LPS <i>V. cholerae</i> Cairo 50 formaldehyde killed	Classical O1 Ogawa
	300 EU LPS <i>V. cholerae</i> Cairo 48 formaldehyde killed	Classical O1
	600 EU_LPS <i>V. cholerae</i> 4260B formaldehyde killed	O139
^x PQ = Pre-qualified by the World Health Organisation (WHO) for purchase by agencies of the United Nations (UN) [*] EU_LPS = ELISA Units of Lipopolysaccharide		

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Table 2: Summary of the meeting presentations on seven campaigns using the oral cholera vaccine (OCV)

Presenters (references)	Dipika Sur (7-10)	Firdausi Qadri (11-12)	Binod Sah (13)	Chris Phares & Kashmira Date	Dang Duc Anh (14-21)	Francisco Luquero (22-24)	Louise Ivers (25-28)
Site	Eastern part of Kolkata, India.	Mirpur, Dhaka (urban) and Keraniganj (rural) in Bangladesh.	Satyabadi block, Puri district, Odisha, India	Mae La Temporary Shelter, Tak Province, Thailand	Vietnam	Boffa and Fore'cariah prefecture in Guinea	Port-au-Prince and Bocozel, Haiti
Type of location	Impoverished urban slums.	Urban and rural settings.	Rural	Refugee camp	Nationwide, both urban and rural settings.	Rural	Urban and Rural
Type of study	Cluster-randomized efficacy study among residents living in 3,933 dwellings (clusters) in Kolkata, India.	A mass vaccination program with Shanchol™ in high risk urban and rural populations in Bangladesh to assess the feasibility of delivery and vaccination utilizing the existing national immunization facilities.	Feasibility study	Public health intervention campaign with KAP surveys regarding cholera, safe water, sanitation, hygiene and cholera vaccine knowledge and acceptability.	Description of how Vietnam has been using OCV in its public health program.	Feasibility, vaccine coverage, and vaccine effectiveness.	Public health intervention to demonstrate the feasibility of delivery of oral cholera vaccine in Haiti, using available doses
Situation	A Phase III trial to study the efficacy of the cholera vaccine.	Biannual epidemics of cholera are seen in many areas of Bangladesh.	Area with endemic cholera.	Seasonal cholera outbreaks in a stable refugee camp.	OCV is one of the vaccines included in the routine schedule of the national EPI.	Coastal and island populations with seasonal cholera outbreaks.	Reactive vaccination, two years into a cholera epidemic in Haiti.
Target group of OCV campaigns	Non-pregnant residents aged ≥1 yr.	All non-pregnant high risk population except those aged <1yr.	Non-pregnant residents aged ≥1 yr. Very sick persons were excluded.	All non-pregnant camp residents aged ≥ yr.	Generally children aged 2-5 years in high-risk areas. In Hue, the vaccine is given to all age groups preemptively. In Hanoi, in 2008, OCV was provided to residents aged > 10 yrs in high-risk districts during an outbreak.	All individuals aged > 1 yr.	All non-pregnant persons aged > 1yr in the target locations.
Number of people targeted for vaccination; number actually received first and second doses (or placebo)	Target population: 108,965 Received at least one dose: 69,308 (64%) Received 2 doses: 67,061 (61%)	Mirpur: Of the 160,000 target population, 141,839 (89%) received the first dose and 123,666 (77%) received the second dose. Keraniganj: Of the 35,000 target population 29,187 (83%) received the first dose and 26,753 (76%) the second dose.	Target population: 51,488: First dose recipients: 31,552 (61%) Second dose recipients: 23,751 (46%)	Target population: 43,968 First dose coverage was high, second dose coverage substantially lower (data presently under analysis). Coverage was lowest among males aged 18–54 years and highest among children aged 1–4 years.	Since 1998, 10.9 million doses of OCV have been provided in the EPI program. The Ministry of Health used additional doses for outbreak control.	Target population: 209,000 Boffa: 89.4% [95%CI: 86.4–91.8%] received the first dose and 79.8% [95%CI:75.6–83.4%] the second dose Fore'cariah: 87.7% [95%CI: 84.2–90.6%] received the first dose and 82.9% [95%CI:76.6–87.7%] the second dose.	100,000 people vaccinated. 90.8% received the second dose of vaccine.

Consent process	Written consent from eligible adults, parents/guardians of minors, and assent from children 12-17 years.	Mirpur: Verbal consent during baseline census and informed written consent before vaccination. Keranigani: Verbal consent during baseline census.	Verbal informed consent/assent was obtained before vaccination.	Verbal informed consent was obtained. Parental verbal informed consent and informed assent procedures for children.	Not applicable – this is part of government program.	Verbal informed consent for the vaccine coverage survey and written consent for the case-control study to measure effectiveness.	The project was a public health intervention, not a research study. No human research consent was obtained. The program was exempted from human subjects review by a national bioethics committee in Haiti. However, a follow up efficacy evaluation of the program is underway (case-control study) and this study has been subject to ethics review. Participants in that study provide consent.
OCV	Shanchol™	Shanchol™	Shanchol™	Shanchol™	ORC-Vax™ and mORC-Vax™	Shanchol™	Shanchol™
Sponsor	B&MGF through the International Vaccine Institute, Seoul, Korea.	B&MGF	B&MGF. Additional funding was provided by the governments of Korea, Kuwait, and Sweden and by the Korea Racing Authority.	Thailand Ministry of Public Health and B&MGF. Implementation through PU-AMI and technical support provided by CDC.	Vietnamese government	<i>Médecins Sans Frontières</i>	American Red Cross and other private donors
Unique features	This was the first study to demonstrate the efficacy of the two-dose regimen of Shanchol™.	These studies are unique as they involve both urban and rural sites. In the urban area, both vaccine and behavior change components were included.	This was the first project undertaken to demonstrate the use of Shanchol™ in a campaign using existing public health program resources.	This is the first evaluation of Shanchol™ in a stable refugee camp setting.	Vietnam is the first and only country in the world to routinely use OCV in its public health program.	This was the first use of Shanchol™ in a mass vaccination campaign in Africa and provides the first estimate of the short-term protection of Shanchol™.	This was the first program using OCV in Haiti.
Major findings	Vaccine protection during the 5 year follow-up period was 65% (one-sided 95%CI lower bound=54%, p<.001). Protection was clearly evident for two years for children vaccinated under the age of 5, but was clearly sustained for 5 years for older subjects.	Mass vaccination is feasible with satisfactory coverage. Analyses are ongoing to determine the effectiveness of OCV (Shanchol™) in decreasing hospitalization due to severe cholera disease.	Mass vaccination is feasible in public health settings but poses challenges on cold chain capacity and human resources at the peripheral health facilities. Campaigns require detailed site-specific micro-planning.	Preliminary analysis of the KAP survey determined the level of community understanding of cholera prevention and treatment, and showed that vaccine acceptability was very high.	Vietnam has been consistently using OCV in their cholera control program since 1998, both preemptively and reactively. Integration of OCV in public health programs is feasible.	The high coverage and good acceptability of the campaigns, conducted in a rural mobile population in Guinea, is encouraging. The percentage of people reporting AEFIs was low and almost all participants reported that they would be vaccinated in a future campaign. This study shows effectiveness of Shanchol™ when used in response to an outbreak in an African country, which supports the addition of vaccination with OCV as an outbreak response tool.	High rate of uptake of vaccine amongst communities, high rate of completion of doses. Field efficacy studies underway.

Abbreviations. AEFI: Adverse events following immunization; B&MGF: Bill & Melinda Gates Foundation; CDC: Centers for Disease Control and Prevention; EPI: Expanded Programme of Immunisation; KAP: knowledge, attitudes, and practices; MoH: Ministry of Health; OCV: oral cholera vaccine; PU-AMI: Première Urgence - Aide Médicale Internationale