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Introducing cholera vaccination in Asia, Africa and Haiti: A meeting report

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ABSTRACT

Orally-administered cholera vaccine (OCV) has been increasingly examined 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.

1. 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 $NaHCO_3$ 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 toward the cost of expanding the stockpile, and endorsed a net budget increase to facilitate increasing the stockpile to 20 M doses of OCV for 2014–2018 [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.

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Table 1
The components of currently available killed orally-administered cholera vaccines.

Trade name, manufacturer, & license	Components	Biotype, serogroup, serotype
Dukoral® SBL Vaccin AB (Sweden)	31.25×10^9 cells *V. cholerae* (heat inactivated)	Classical O1 Inaba
Licensed (1991)	31.25×10^9 cells *V. cholerae* (formalin inactivated)	El Tor O1 Inaba
PQ (2001)	31.25×10^9 cells *V. cholerae* (heat inactivated)	Classical O1 Ogawa
Recombinant cholera toxin B subunit (rCTB) 1 mg (from *V. cholerae* O1 Inaba, classical biotype strain 213.)	31.25×10^9 cells *V. cholerae* (formalin inactivated)	Classical O1 Ogawa
Orally administered as 3 ml in 150 ml $NaHCO_3$ per dose		
ORC-Vax, NIHE, Hanoi,	2.5×10^{10} cells *V. cholerae* Phil 6973 formalin killed	El Tor O1 Inaba
Vietnam Formulation 1:	2.5×10^{10} cells *V. cholerae* Cairo 50 heat killed	Classical O1 Ogawa
Licensed in Vietnam (1997)	2.5×10^{10} cells *V. cholerae* classical 569B formalin killed	Classical O1 Inaba
	2.5×10^{10} cells *V. cholerae* classical Cairo 48 heat killed	Classical O1 Inaba
	2.5×10^{10} cells *V. cholerae* 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam	5.0×10^{10} cells *V. cholerae* Phil 6973 formalin killed	El Tor O1 Inaba
Formulation 2: Licensed in	2.5×10^{10} cells *V. cholerae* Cairo 50 heat killed	Classical O1 Ogawa
Vietnam (1997)	2.5×10^{10} cells *V. cholerae* classical 569B formalin killed	Classical O1 Inaba
	2.5×10^{10} cells *V. cholerae* classical Cairo 48 heat killed	Classical O1 Inaba
	5.0×10^{10} cells *V. cholerae* 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam	5.0×10^{10} cells *V. cholerae* Phil 6973 formalin killed	El Tor O1 Inaba
Formulation 3: Licensed in	2.5×10^{10} cells *V. cholerae* Cairo 50 heat killed	Classical O1 Ogawa
Vietnam (2000)	2.5×10^{10} cells *V. cholerae* classical 569B formalin killed	Classical O1 Inaba
	2.5×10^{10} cells *V. cholerae* 4260B formalin killed	O139
mORCVax, Vabiotech, Vietnam	600 EU LPS* *V. cholerae* Phil 6973 formalin killed	El Tor O1 Inaba
Formulation 4: Licensed in	300 EU LPS *V. cholerae* Cairo 50 heat killed	Classical O1 Ogawa
Vietnam (2009)	300 EU LPS cells *V. cholerae* classical Cairo 48 heat killed	Classical O1 Inaba
	600 EU_LPS *V. cholerae* 4260B formalin killed	O139
Shanchol® Licensed in India	600 EU LPS *V. cholerae* Phil 6973 formaldehyde killed	El Tor O1 Inaba
(2009) [X]PQ (2011)	300 EU LPS *V. cholerae* Cairo 50 heat killed	Classical O1 Ogawa
Orally administered as 1.5 ml	300 EU LPS *V. cholerae* Cairo 50 formaldehyde killed	Classical O1 Ogawa
suspension per dose	300 EU LPS *V. cholerae* Cairo 48 formaldehyde killed	Classical O1
	600 EU_LPS *V. cholerae* 4260B formaldehyde killed	O139

[X] PQ = Pre-qualified by the World Health Organization (WHO) for purchase by agencies of the United Nations (UN).
* EU_LPS = ELISA units of lipopolysaccharide.

2. 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 10 m 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.

3. 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