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How can controlled human infection models accelerate clinical development and policy pathways for vaccines against *Shigella*?

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ABSTRACT

Controlled Human Infection Models (CHIMs) now exist for several infectious diseases. CHIMs offer significant insight into disease pathogenesis, as well the potential to rapidly test clinical proof-of-concept of vaccine candidates. The application of CHIMs to identify a correlate of protection that may reduce the sample size of, or obviate the need for clinical efficacy studies to achieve licensure is of considerable interest to vaccine developers and public health stakeholders. This topic was the subject of a workshop at the 2018 Vaccines Against Shigella and ETEC (VASE) conference, in the context of O-antigen-based *Shigella* vaccines.

1. Introduction

The use of Controlled Human Infection Models (CHIMs) to inform vaccine development is expanding with several review articles summarizing their application against a broad range of pathogens, including bacteria, viruses, parasites and helminths [1,2]. CHIMs have several applications, including investigating the natural history of disease and disease pathogenesis, with the objective of identifying immune correlates of protection (CoP). Evaluation of a candidate by CHIM in early clinical development provides a signal of efficacy and is commonly used to down-select or prioritize vaccine candidates. If the challenge model and its associated reagents and assays are standardized, and the immune response that is required to prevent disease are well characterized, it may be possible to identify an immunological threshold that is associated with protection in the CHIM. However, CHIMs are limited in that the test population may not be immunologically representative of the target population and the inoculation routes and infectious strains may differ, so the level of protection demonstrated in the controlled conditions of a CHIM are not necessarily recapitulated in field efficacy studies. A putative correlate in the CHIM will likely need to be confirmed, and ultimately validated, through field efficacy trials. If there appears to be evidence for a correlate (or surrogate) of protection in a CHIM that is supported by an initial field efficacy study (typically a phase 2b study), many stakeholders are asking whether the inclusion of CHIMs in the clinical development strategy of a vaccine has the potential to reduce the sample size and duration of the pivotal efficacy study to support licensure. The cost and logistical difficulties associated with undertaking large field efficacy trials make this aspect of CHIM utility particularly attractive, and such an approach would significantly de-risk investment in late-stage product development. For this reason, the potential application of CHIM to accelerate licensure of vaccines has resulted in significant interest from product developers, and has been discussed in several recent fora and conferences, including the previous 2016 VASE meeting [3], the 2017 International Alliance for Biological Standardization meeting [4] and at a 2017 consultation in Malawi [5].

The precedence for licensure on the basis of CHIM data without field efficacy data, comes from the recent FDA approval of Vaxchora, a vaccine for the prevention of cholera in 18–64 year old travelers to cholera-affected areas. Vaxchora's efficacy was demonstrated in a randomized, placebo-controlled human challenge study of 197 cholera-naïve U.S. volunteers from 18 through 45 years of age [6]. It was shown to be 90% efficacious among those

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challenged 10 days after vaccination and 80% among those challenged three months after vaccination. An immune response associated with protection in the CHIM study was demonstrated in the 18–64 year old age group, and safety was evaluated in a separate study of 3235 participants of 18–64 years. Collectively these data were the basis for the extension to and approval in 18–64 year olds. However, the vaccine is limited to use in adult travelers. Its effectiveness in populations living in endemic areas is not known, and it is not licensed for that indication.

More recently, CHIM data were used to support a WHO policy recommendation for the use of the typhoid conjugate vaccine, Typbar-TCV, in infants and children from 6 months of age and in adults up to 45 years in typhoid endemic regions [7]. The Typbar-TCV vaccine is based on Vi-polysaccharide (Vi-PS) conjugated to tetanus toxoid, Vi-TT, and was licensed in India on the basis of serum Vi antibody responses in children and adults. The Typbar-TCV demonstrated an immune response that was superior for Vi-TT after 2 years and only one dose, including in 6 month olds [8]. Although a conjugate of the Vi bound to recombinant exoprotein A of Pseudomonas aeruginosa (Vi-rEPA) was shown to enhance Vi immunogenicity and protect 2- to 5-year-olds in Vietnam [9], there were no phase 3 efficacy data available with the Vi-TT vaccine. Prior to developing the WHO recommendation for the Vi-TT vaccine, this evidence gap was addressed by a CHIM study in 18–60 year old adults to bridge the immunogenicity and efficacy between the Vi-TT and Vi-PS vaccines [10]. In this study, the Vi-TT candidate demonstrated 87.1% (95% CI 47.2–96.9) efficacy compared with 52.3% (95% CI: −4.2 to 78.2) for Vi-PS vaccine based on an endpoint of fever and positive blood culture, with 100% seroconversion in Vi-TT group versus 88·6% in Vi-PS participants. Significantly higher geometric mean titers of IgG to Vi were detected 1-month post-vaccination in Vi-TT vaccinees as compared with Vi-PS recipients. Large scale trials to formally assess the efficacy and effectiveness of Typbar-TCV are underway, however results from these studies will not be reported for several years.

With these examples as context, there is considerable interest in how CHIM can accelerate licensure for Shigella vaccine candidates. According to the Global Burden of Disease estimates, *Shigella* is the second most deadly diarrhoeal disease, causing approximately 212,438 deaths (95% UI 136 979–326 913) per year, globally [11]. Of these, 63,713 deaths (41 191–93 611) are in children under five years of age, the majority of which are in low- and middle-income countries. *Shigella* also causes inflammation leading to growth faltering, contributing to its position among the top 4 causes of diarrhea-associated YLDs globally [12]. Increasingly resistant to treatment with antibiotics, *Shigella* is on the WHO AMR priority list [13]. In addition, WHO's Product Development for Vaccines Advisory Committee (PDVAC) has identified *Shigella* vaccines that reduce diarrhea, dysentery and morbidity in children under 5 years of age, as a priority from the perspective of LMICs [14].

Proof of concept for field efficacy of O-antigen-based *Shigella* vaccines was established over 20 years ago with a first-generation conjugate vaccine composed of *Shigella* sonnei O-specific polysaccharide bound to *Pseudomonas aeruginosa* recombinant exoprotein A (*S. sonnei*-rEPA). This candidate elicited protective antibodies against surface O-Ag of lipopolysaccharide [15]. However, O-Ag antibody responses, and the protection observed decreased with the age, and while efficacy of 71% percent was observed in 3–4 years olds, no efficacy was observed in the target age group of infants and toddlers [16]. There are three new-generation conjugate/O-antigen-based vaccines currently in clinical development, utilizing three different manufacturing platforms. In naive adults, these appear to be more immunogenic than the historical candidates. It is hoped that the new candidates will demonstrate improved immunogenicity and efficacy in the target population of young children in LMICs. A key question from stakeholders involved in product development is whether CHIM may accelerate their development by confirming efficacy and establishing an immunological threshold of serum O-Ag IgG antibody that could offer protection.

A workshop to consider the role of CHIMs in clinical development for vaccines against *Shigella*, and specifically the potential of CHIM to accelerate licensure in LMICS, was held at the 2018 Vaccine against Shigella and ETEC conference in Mexico City. This report summarizes those discussions.

1.1. Status of Shigella candidates in development

The *Shigella* vaccine pipeline currently contains a number of vaccines that are in phase 1 and 2 clinical trials. The leading candidates are O-antigen-based vaccines designed to induce a protective immune response through the induction of serum IgG to O-antigen. They have been developed and tested initially as monovalent vaccines against *S. flexneri* 2a or *S. sonnei*, prior to expansion into quadrivalent formulations necessary to confer broad coverage with components most commonly targeting *S. sonnei* and *S. flexneri* 2a, 3a and 6 [17].

One candidate is a bioconjugate vaccine consisting of *Shigella* O-antigen covalently linked to tetanus toxoid as carrier within genetically-engineered *E. coli*. A monovalent *S. flexneri* 2a bioconjugate was tested in a phase 1 study in the US [18] and CHIM study at Johns Hopkins University [19]. The quadrivalent version of the vaccine will enter a phase 1/2a age-descending study into the target population in Africa in 2019. Another candidate is a vesicle-based vaccine (termed 'GMMA'). Monovalent *S. sonnei* candidate GAHB1790 was tested in phase 1 studies in France and the UK [20] prior to a phase 2a study in Kenyan adults [21]. It is currently being assessed in a CHIM study in Cincinnati while a quadrivalent vaccine is being produced for a similar phase 1/2a age-descending study as planned for the four-valent bioconjugate.

A monovalent *S. flexneri* synthetic O-antigen conjugate vaccine with tetanus toxoid as carrier has been tested in a phase 1 study among Israeli adults [22] and further trials are planned, including a CHIM study of the monovalent vaccine at the University of Maryland, alongside the development of a multivalent vaccine. Other vaccines in clinical trials include the Invaplex vaccine developed by the Walter Reed Army Institute for Research [23,24]. This consists of a physical mixture of *Shigella* lipopolysaccharide and Ipa proteins. Several live attenuated vaccines have also been tested in early clinical trials. The key objective of the workshop was to discuss the feasibility of using CHIM to advance these vaccines based on the concept of serum IgG to O-antigen as a correlate of protection and establishment of an immunological bridge to historical efficacy studies with the early conjugate vaccines [15,16].

1.2. CHIMs for Shigella vaccine development

The potential of CHIM to accelerate clinical development and policy pathways for *Shigella* vaccines is greatly assisted by a half-century of *Shigella* CHIM development and refinement. Findings from the first iteration of the model, performed at the University of Maryland using *S. flexneri* 2a strain 2457 T, were reported in 1946 [25]. Symptoms mimicked natural infection, but attack rates were not reproducible among volunteers. The use of bicarbonate buffer prior to ingestion of the *Shigella* challenge doses ameliorated this situation, leading to reliable attack rates with around 1500 bacilli [19].

The *Shigella* CHIM has now been established in three centers in the USA: University of Maryland, Johns Hopkins University and Cincinnati Children's Hospital and Medical Center. Challenge is possible with both *S. flexneri* 2a 2457 T and *S. sonnei* strain 53G, and GMP lots of both strains have been produced and are available

for use. Studies over the last 50 years have demonstrated that the *Shigella* CHIM is safe for participants and rapid resolution of symptoms occurs following antibiotic treatment.

The three sites currently conducting CHIM are all situated in the USA, a high-income country, leading to discussion as to the potential value of establishing *Shigella* CHIM in LMIC settings. There is precedence for this with the S. sonnei 53G strain that was established by the Mahidol University in Bangkok, Thailand [26]. However, the presence of high levels of pre-existing specific antibodies to *Shigella* in LMICs where shigellosis is endemic is likely to require the use of higher levels of *Shigella* bacilli to cause illness than in non-endemic HIC contexts. The variability in the level of pre-existing antibodies, depending on exposure, is likely to present issues for ensuring an adequate attack rate and reproducibility in LMIC CHIM, as was observed at the Mahidol site. Therefore, the current situation where US adults are challenged with wild-type *Shigella* may be more representative of the target population of LMIC children than initially appreciated, since both are immunologically-naïve to *Shigella*. However it has not been possible to reliably characterize and compare responses in these different contexts because the CHIM methodology and its associated assays are not standardized. For CHIM studies to be fully leveraged to inform vaccine development, there is a need for the harmonization of protocols, sample collection and clinical endpoints. This has been addressed by workshops and working groups over the past year, with consensus reached among investigators from the three *Shigella* CHIM centers. Publication of these consensus positions is planned for 2019.

There was passionate discussion around the feasibility of conducting *Shigella* CHIM among LMIC children in view of their status as the target population and absence of pre-existing immunity. Performing research involving children requires that the investigator and the research ethics committee ensure that a parent or a legally authorized representative of the child has given permission, and that the child has given agreement (assent), after having been provided with information that has been appropriately tailored to the child's level of maturity [27]. Broadly speaking, workshop participants fell into two groups, the larger of which viewed CHIM studies in LMIC children as being unethical, particularly since children are considered a vulnerable group, and because a CHIM study involves exposure that carries inevitable health risk without certain benefit. However, a minority of participants argued that since children die from shigellosis in vaccine field trials, it is no less ethical to conduct *Shigella* CHIM in children than it is to conduct a field efficacy study. It could be positioned that undertaking CHIM in children in LMICs is ethically justifiable, because of the greater probability of infection (risk) in those contexts, the opportunity to gain immunity to subsequent wild-type infections in a well-controlled, relatively safe environment and the need understand the potential benefits to that specific population.

Ultimately, the discussion returned to the necessity for a *Shigella* efficacy trial in the target population of young children, since the community does not currently have an established surrogate marker or correlate of protection. Targeting sites with high shigellosis attack rates could mitigate against excessively large trial sizes.

2. Potential product development strategies

The first quadrivalent *Shigella* vaccine candidate is expected to enter phase I/2a clinical trials in 2019 and will evaluate safety and immunogenicity of all four components. The study will be performed in adults and age de-escalate to infants and toddlers in a LMIC, with the objective of determining the optimal dose and schedule in this target population. Progression to field testing of the quadrivalent is likely to be contingent on demonstration of efficacy of at least one component in a CHIM study, i.e. against either the *sonnei* or *flexneri* 2a strains for which CHIM are available. If the end-points of the Phase 1/2a are met, the candidate could progress to a larger Phase 2b safety and immunogenicity study in 6–12 month olds in LMICs, with an adaptive trial design to transition to phase 3 following an interim analysis for futility. The phase 3 study would assess efficacy against shigellosis in the target population, envisaged to support a licensure application to either the European Medicines Agency, or the US Food and Drug Administration, or both.

The notion of utilizing the CHIM model to allow immunobridging between current clinical candidates and historic *Shigella* efficacy studies is fundamentally based on establishing serum O-antigen IgG threshold as a correlate of protection, and triangulating the protective titer between the historical candidate, the CHIM model, and the titers induced by the new candidates in field testing. This correlate threshold may also be informed by sera from children convalescing from natural infection. The approach requires development of a standardized O-antigen ELISA and development of international standards to be able to compare immunological responses in different laboratories and settings. Work on both CHIM harmonization and O-antigen ELISA standardization is already underway. It is important to note that while CHIMs have good potential to identify correlates of protection against shigellosis, the limited time between immunization with a candidate vaccine and bacterial challenge inevitably means that any such correlates will indicate short-term but not necessarily long-term protection. For long-term protection, other facets of the immune responses may be important to assess, such as memory B cells and T-follicular helper cells.

Assuming that a correlate of protection can be identified utilizing the CHIM, and this immunological threshold is achieved in clinical studies and supported by titers in convalescent sera, three potential licensure routes are conceivable based on different clinical development strategies:

1. Licensure of a travelers' vaccine in adults, based on CHIM (*S. sonnei and S. flexneri 2a*) and the phase I/2a data with the quadrivalent candidate, assuming a sufficient safety database.
2. Accelerated licensure of a vaccine for adults and children, including infants, based on CHIM (*S. sonnei* and *S. flexneri 2a)* and phase I/2a data with the quadrivalent candidate, plus safety, immunogenicity and indicative efficacy data from the Phase 2b study in the target population. This route assumes a sufficient safety database in infants, and may enable use of the vaccine in private markets and non-military travelers, but would likely not enable access and use through immunization programmes of LMICs. In this scenario, efficacy data may be collected post licensure, but would need data from LMICs to support use in these target populations.
3. Traditional licensure for infants in LMICs, based on demonstration of efficacy against shigellosis by at least one of the four *Shigella* components of the candidate, most likely targeting *S. sonnei* or *flexneri* 2a. The candidate is unlikely to be able to generate efficacy data against the 3a and 6 serotypes as their incidence is too low. For vaccines that are intended for markets outside the EU, and in cases where the vaccine would address a priority unmet medical need, the EMA in cooperation with the WHO, can provide scientific opinions through its Article 58 procedure. This has the benefit of rigorous scientific assessment to the same standards as for medicines intended for use in Europe, but with involvement of experts from WHO and national regulatory authorities in target countries as well as streamlined assessment under the WHO prequalification programme. However, the Article 58 procedure provides scientific

opinion only on vaccines that are intended exclusively for markets outside of the European Union, and so could not be applied to a vaccine that had previously been licensed for travelers.

An additional question facing product developers, regulators and ultimately policy makers, is (how) can utilization of CHIM accelerate the route to *uptake* in LMICs? It seems that there could be a role for CHIM in supporting licensure, as has been demonstrated in the cases of OCV and other vaccines, but it is not clear what impact this would have on facilitating a policy recommendation, particularly considering that the CHIM-based accelerated routes will generate less efficacy data than conventional routes. If countries require data in their populations to determine whether or not to introduce a vaccine, licensure based on an immunological correlate rather than efficacy may potentially delay access and introduction.

3. Regulatory considerations for the use of CHIM in licensure of vaccines for LMICs

The regulatory framework for challenge trials was reviewed recently by The International Alliance for Biological Standardization [4]. In brief, the US FDA reviews CHIM studies under an Investigational New Drug (IND) application, however the European Medicines Agency does not; in the European Union, the review and approval of CHIM studies are under the purview of the individual Member States. Although there is acknowledgement that CHIM studies facilitate comparison of candidates and prioritization decisions, consensus regarding the role of CHIM in licensure and explicit guidance from regulators are not yet available. WHO has published guidance on regulatory considerations for national regulatory authorities (NRAs), manufacturers and vaccine developers, and will assist in the implementation of the guidelines through workshops, training and advisory groups [28]. However, the generally-held position is that CoPs identified in a CHIM would need to be validated in a clinical efficacy study, particularly since CHIM studies are performed in naive adults and typically in high income countries, and it is not predictable how data from these studies may extrapolate to infants in LMICs. Therefore the generally-accepted view at this point in time is that there remains a need to demonstrate efficacy in randomized controlled trials. However, *Shigella* vaccine developers are advised to seek scientific advice (within or without the context of an article 58) from the regulatory authorities to discuss possible options and to plan accordingly. This will be particularly important for a strategy that envisages an Article 58 submission, since the EMA does not have guidelines on CHIM.

Even if demonstration of efficacy by CHIM is not able to replace lengthy and cost-prohibitive phase 3 studies, they will contribute supportive data for licensure, and may be able to reduce the size of the primary end-point requirement and/or scope of a field efficacy study, for example by demonstrating efficacy against one or more vaccine components for which demonstration of field efficacy is not possible.

4. The end-goal: vaccine policy recommendation for use in LMICs

The end goal for vaccines that are developed for use in the immunization programmes of LMICs is not licensure. It is to ensure and expedite uptake and impact in populations with the highest disease burden. To achieve vaccine financing and introduction in LMICs, there are several other pre-requisite steps that need to be undertaken, including a WHO policy recommendation and WHO prequalification [29]. WHO evaluates data to develop evidence-based immunization policy recommendations that provide guidance to its Member States on health policy matters. These recommendations are informed by an independent advisory group, the Strategic Advisory Group of Experts (SAGE) on Immunization, that provides guidance to WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and linkages with other health interventions. The committee meets biannually to review and critically appraise the available evidence on vaccines that are licensed or approaching licensure, and other immunization-related topics, and to formulate recommendations. While licensure evaluates the safety, quality and efficacy of a vaccine, a policy recommendation considers broader aspects including vaccine effectiveness and impact, which are affected by feasibility of implementation and the ability of the vaccine to meet coverage and equity targets. Vaccine effectiveness refers to the direct (vaccine-induced) and indirect (population based) protection during routine use, and is a key consideration for both policy recommendations, and introduction decisions by countries. Therefore, although CHIMs may accelerate the route the licensure, the timeline to access by LMICs may be delayed without a clear commitment to fund the efficacy and effectiveness studies that will be necessary, post-licensure.

WHO vaccine position papers summarize essential background information on the respective diseases and vaccines, and importantly present the WHO position in the global setting to assist Member States in their deliberations regarding vaccine introduction, under the auspices of their respective national immunization technical advisory group (NITAG) [30]. Other technical and global advisory committees support the work of SAGE, including PDVAC. PDVAC was established in 2014, and its mission is to accelerate product development of vaccines and technologies that are urgently needed and ensure they are appropriately targeted for use in low- and middle-income contexts. It focuses on pathogen areas with candidate vaccines or technologies, generally at the Phase 2 stage of clinical evaluation or earlier, and prior to the development of WHO policy on use. Increasingly, PDVAC is seeking to work with relevant stakeholders, including SAGE and end-users, in early clinical development to evaluate the pathway beyond product licensure, to policy recommendation. The intent of this earlier engagement is to ensure that the appropriate data relevant to SAGE and LMIC policy makers are generated as part of the licensure strategy, to avoid a delay between licensure and country uptake, as has been the case for other recently licensed vaccines [31,32].

One example of a product that has experienced a significant delay between licensure and development of a programmatically appropriate presentation is oral cholera vaccine (OCV). The first OCV, Dukoral®, was licensed for travelers in Sweden in 1991, and granted a Marketing Application Authorization by the EU in 1994. In its first cholera vaccine position paper, published in 2001, the WHO solely recommended the pre-emptive use of OCV in high-risk populations [33], however the WHO also stated that "the current internationally-available pre-qualified vaccine (Dukoral) is not recommended once an outbreak of cholera has started" [34]. It wasn't until the availability of a more programmatically suitable presentation of the vaccine, Shanchol™, became available, that the WHO position was updated in 2010 "to consider the use of oral cholera vaccines in reactive situations" [35]. In 2013, an OCV stockpile was created, which provided a market incentive to manufacturers and provided a signal to continue to optimize the product. In 2015, single doses of OCV in preformed plastic tubes became available [36], known as Euvichol®. This product is being further optimized for use within a controlled temperature chain, which means that it can be used outside of the cold chain for up to 3 days and withstand temperatures of 40℃, thereby significantly easing vaccine delivery in humanitarian emergencies, outbreaks and endemic areas. Improvements in the vaccine presentation have

driven demand for the vaccine; between 1997 and 2012, 1.5 million doses of cholera vaccine were used worldwide, but in 2017 alone, this had increased to 10 million doses. However, this level of uptake has taken 26 years, from when the vaccine was first approved. This example underscores the importance of understanding the needs of countries during the product development, in order to understand what data are needed to support a policy recommendation immediately following licensure.

5. Discussion

The development of vaccines against *Shigella* is a public health priority. *Shigella* causes approximately 212,000 deaths per year, globally, with a disproportionate mortality and morbidity burden in infants and young children living in LMICs. The rise in antibiotic resistance by *Shigella* species has become a global issue and a vaccine is urgently needed. However, the heterogenous epidemiology of *Shigella* means that vaccine efficacy studies will likely be large, multi-center trials, and the vaccine, once it becomes available, is likely to be deployed on a regional or sub-national basis. In order to reduce the timeline, cost and risk of product development, global stakeholders are seeking innovative routes to licensure to help incentivize development of a vaccine against this deadly disease.

The CHIM has played a role in the development and licensure of several vaccines, and is a valuable tool in the assessment of pipeline candidates for numerous pathogens. While not necessarily recapitulating wild-type infection, CHIMs offer the opportunity to identify correlates of protection that can facilitate candidate evaluation and may inform clinical development and regulatory strategies for novel vaccines, including dose and schedule finding. They generally involve only tens of subjects, require only a few months to complete and can generate human proof of concept data with speed, efficiency and minimal expense. However, CHIM do not have the same level of robustness as field efficacy studies and are currently considered as supportive evidence in a license application. This being said, there is significant engagement among product developers, regulators, ethicists and funders – across several disease areas - to understand if and how CHIM can accelerate regulatory approval and uptake of vaccines in LMICs.

In the case of *Shigella*, work is underway to standardize the CHIM model methodology and to develop reference reagents. This will be needed to establish a threshold serological response that is associated with protection conferred by a historical vaccine candidate. The new generation O-Ag based *Shigella* candidates are still in early clinical development, and although CHIM have provided clinical proof of concept for protection against shigellosis, these studies were performed in naive adults in high income countries (HIC). During this workshop, the potential for and relevance of CHIM studies in LMICs, and in particular in pediatric populations within LMICs, was explored. The immunological responses from CHIM performed in these settings are likely to be more representative than that from HIC considering the differing host-pathogen relationships, microbiota and levels of pre-existing immunity, and therefore could significantly accelerate and de-risk product development. However, the counter argument is that naive adults are a good model for newborn infants who have not yet had exposure to environmental pathogens. The use of CHIM for malaria is established in Tanzania, and more recently in Gabon and Kenya, however none of these studies involve children.

In view of the regulatory and ethical considerations for performing CHIMS in children, which do not offer individual benefit, this approach requires a compelling rationale, i.e. it would only be contemplated in the event that an alternative pathway to demonstrate efficacy in the target population was not feasible. This is not the case for the development of *Shigella* vaccines. However, there may be innovative and ethical strategies to use a challenge-based approach in infants, as was reported in the recent parenteral rotavirus vaccine trial in South Africa [37]. Following immunization with 3 doses of the experimental non-replicating rotavirus vaccine (NRRV), neutralizing antibody responses were found to be over 80% for P8 strains and 30–50% for P6 strains. Participants received licensed Rotavirus vaccine (human attenuated) one month after the third dose of NRRV, and virus excretion was then evaluated by ELISA at days 5, 7 and 9. Vaccine shedding was reduced in the NRRV-vaccinated children, suggesting that the parenteral vaccine may be acting at the mucosal surface to prevent replication of the attenuated vaccine, and this may be a proxy for efficacy. In general, the workshop participants were keen to further explore novel applications for CHIM in the context of *Shigella* vaccine development, particularly since there is strong optimism that the immune responses to the next generation O-Ag based candidates in children will be superior to that of the historical, partially efficacious vaccine.

With this in mind, experts in the *Shigella* community have begun collaborating to map out potential regulatory scenarios utilizing CHIM, and in the event that a correlate can be established, to understand how this may be used to expedite the route to licensure. However, stakeholders must bear in mind that the end goal is beyond vaccine licensure by EU or US regulators, and that this vaccine will have the most impact in LMICs if it receives a policy recommendation from WHO for use. This recommendation is a pre-requisite for WHO prequalification as well as financing by Gavi to enable vaccine procurement, and ultimately vaccine introduction and access. In preparation for approval and uptake in LMICs, it will be important to further familiarize LMIC regulators with CHIMs.

The conclusion from this workshop was that various product development scenarios should be developed now, including those that propose CHIM as the basis for, and/or supportive of licensure, and to facilitate proactive discussion with global regulators. In addition, the stage-gates, costs and timelines for each scenario need to be articulated to support discussions with manufacturers, including those in LMICs who also need to be engaged. Fundamental to this scenario planning will be determining the clinical trial sites with appropriate epidemiology to perform the phase 2b/3 adaptive efficacy study, the design, cost and timeline for which will be impacted by factors including disease attack rate, levels of pre-existing immunity and circulating serotypes. The hope is that by considering the benefits and pitfalls of these respective scenarios early on, from the perspective of drivers that favour a future policy recommendation (as well as licensure), this will reduce the gap between vaccine licensure and vaccine access – known as the implementation gap, for vaccines.

Conflict of interest

None declared.

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