Vaccine 37 (2019) 7381–7390

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO consultation on ETEC and *Shigella* burden of disease, Geneva, 6–7th April 2017: Meeting report

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ARTICLE INFO

Article history:
Available online 17 January 2018

Keywords:
Enterotoxigenic *E. coli*
ETEC
Shigella
Vaccine
Mortality
Burden of disease

ABSTRACT

According to the 2015 Global Burden of Disease Study, diarrhea ranked ninth among causes of death for all ages, and fourth among children under 5 years old, accounting for an estimated 499,000 deaths in this young age group. It was also the second most common cause of years lived with disability (2.39 billion YLDs). The goal of the WHO/UNICEF Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) is to reduce deaths from diarrhea in children under 5 years of age to less than 1 per 1000 live births, by 2025. Development of new and improved vaccines against diarrheal infections is a fundamental element of the strategy towards achieving this goal.Enterotoxigenic *Escherichia coli* (ETEC) and *Shigella* are enteropathogens that cause significant global mortality and morbidity, particularly in low- and middle-income countries. In 2016, WHO's Product Development for Vaccines Advisory Committee (PDVAC) recommended that the WHO's Initiative for Vaccine Research (IVR) engage in this area, based on PDVAC's criteria of prioritizing the development of vaccines against pathogens that will address a major unmet public health need, and for which clinical candidates with a good probability of technical success are in the pipeline. As a first step, WHO's IVR convened global subject matter experts to discuss the current global ETEC and *Shigella* disease burden estimates, including the current understanding of the long-term indirect effects of ETEC and *Shigella* infection, and how these data may affect future decision making on vaccine development for both pathogens.

The available global burden estimates for ETEC and *Shigella* differ with respect to the relative importance of these two pathogens. The mortality estimates vary between iterations published by the same group, as well as between estimates of different groups, although the uncertainty intervals are broad and overlapping. These variances are attributable to differences in the data available and incorporated in the models; the methods used to detect the pathogens; the modelling methodologies; and, to actual changes in the total number of diarrheal deaths over time. The changes in the most recently reported mortality estimates for these pathogens, as compared to previous iterations, has led to debate as to whether investment in development of stand-alone vaccines, rather than combined vaccines, is warranted from cost-effectiveness and vaccine impact perspectives. Further work will be needed to understand better the variances and uncertainties in the reported mortality estimates to support investment decision making, and ultimately policy recommendations for vaccine use. In addition, a comprehensive assessment of the value proposition for vaccines against these pathogens is needed and will be strengthened if the long-term health consequences associated with diarrhea and dysentery due to these pathogens are better defined.

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https://doi.org/10.1016/j.vaccine.2017.10.011
0264-410X/

1. Introduction and objectives of the consultation

Between 2005 and 2015, global deaths due to diarrhea are estimated to have decreased by 34.3% and 20.8% among children younger than five years and people of all ages, respectively. These reductions were due, in part, to the widespread introduction of rotavirus vaccine for infants [1]. However, some diarrhea pathogens, including ETEC and *Shigella,* are still considered substantial causes of mortality and morbidity, particularly among infants and young children in low and middle-income countries (LMICs), as well as morbidity in travelers and military personnel from higher income countries [2–6]. The global burden of pathogens causing diarrhea predominantly lie in children under five years (U5) in sub-Saharan Africa and South Asia, where a large proportion of the population has poor access to primary healthcare, clean water and sanitation [1]. Conventional treatment regimens include the use of oral rehydration salts (ORS) and, where appropriate and available, the use of antimicrobials [7]. However, with the emergence of multi-drug resistant strains of ETEC and *Shigella*, the public health need for vaccines against these pathogens is likely to increase [8,9].

The Institute for Health Metrics Evaluation (IHME) reports the Global Burden of Disease (GBD) estimates. Its two most recent evaluations of diarrhea burden (for the years 2013 and 2015) have incorporated studies that use molecular detection methods to attribute etiology, instead of using only culture based data [6,10]. Quantitative PCR increased detection of *Shigella* (twofold) and heat-stable type toxin producing ETEC (1.5-fold) compared to culture-based methods [11]. This change in detection methodology since the 2010 GBD iteration has contributed to variations in the GBD reported pathogen-attributable disease burden [12] (Tables 1 and 2). In the GBD 2015 estimates, the all-age *Shigella* disease burden has increased markedly compared to that for 2010, and is now double that attributable to ETEC, at 164,300 (95% Uncertainty Interval (UI) 85,000–278,700) vs. 74,100 (UI 29,900–137,900) deaths in 2015, respectively (Table 1). The same pattern is observed in the U5 age group, between 2013 and 2015; the estimated *Shigella* attributable mortality burden is approximately double that of ETEC at 54,900 (UI 27,000–94,700) vs 23,600 (UI 9600–44,300) deaths in 2015, respectively (Table 2). The recent changes in the burden estimates, due, at least in part, to changes in detection and modelling methodology, pose challenges for vaccine developers, funders and policy makers in prioritizing the relative importance of intervention strategies against ETEC and *Shigella*.

In addition to the IHME GBD estimates, the Maternal and Child Epidemiology Estimation (MCEE) group also reports global mortality estimates [5,13]. In 2013, MCEE (previously known as CHERG) published estimates of pathogen-specific mortality for children U5 of age using etiologic data from hospital inpatient studies as a proxy for the pathogen distribution. These estimates were based on studies that used conventional pathogen detection techniques. MCEE estimates (Table 2) suggest that ETEC mortality is higher than *Shigella* in the U5 age group, at approximately 42,000 (UI 20,000–76,000) vs 28,000 (UI 12,000–53,000) deaths in 2011, respectively, the converse from U5 estimates reported by IHME in 2015. In terms of numbers of *Shigella* deaths, the 2011 MCEE estimates are half those of IHME for the year 2015.

Each disease burden model has its strengths and limitations. Factors such as inclusion/exclusion criteria, model inputs and adjustments, assessment of pathogenicity, geographical representativeness, and country or regional extrapolation affect conclusions about attributable burden. There are three genotypes of ETEC based on the presence of toxin genes responsible for production of heat stable toxin (ST-ETEC), heat labile toxin (LT-ETEC), or both. Neither estimate accounted for these different toxinotypes despite observations that strains producing ST alone or in combination with LT produce more severe disease. Furthermore, modelling methods and diagnostic methods are continually undergoing optimization, resulting in variation of the estimates for each iteration.

In addition to the ETEC and *Shigella* mortality highlighted by the IHME and MCEE estimates among children, it is worth noting that both pathogens are associated with significant mortality across all ages (Table 1) [14]. This observation is consistent with other studies, such as that reported by the Foodborne Disease Burden Epidemiology Reference Group (FERG), indicating that the diarrheal disease burden remains high in older age groups living in LMICs, and, in particularly high-risk areas, like WHO AFRO and SEARO regions, ETEC and *Shigella* disease rates are estimated to be substantially higher than those for cholera or typhoid fever [15].

Several additional key epidemiological studies continue to contribute to, and are expected to refine, future mortality and morbidity estimates. The Global Enteric Multi-Center Study (GEMS) [16] and the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) [17] are two large epidemiologic studies that have been instrumental in informing disease etiology and quantifying pathogen-specific diarrheal disease burden in LMICs. Results from these studies will be incorporated into the next iteration of GBD and MCEE estimates. The expanded introduction of rotavirus vaccines is anticipated to impact the etiology attributed to diarrheal disease and the relative importance of other pathogens as causes of clinically significant diarrhea [18]. The rotavirus Vaccine Impact on Diarrhea in Africa (VIDA) study is an ongoing case-control study to evaluate the incidence, etiology, and sequelae of moderate-to-severe diarrhea in three of the African GEMs sites after rotavirus vaccine introduction (see Section 3).

Mortality is considered a major criterion for informing decisions regarding vaccine development, policy recommendations, global financing and procurement of vaccines in LMICs [19]. For this reason, the GBD-reported increase in estimated *Shigella*-attributable mortality, together with its notably lower estimates of ETEC-attributable mortality, has led some stakeholders to re-evaluate their investments in ETEC and *Shigella* vaccine development. The estimates reported by IHME, however, are not necessarily reflected in other published estimates. Therefore, while there is general agreement that ETEC and *Shigella* are both significant causes of diarrhea, there is not a clear consensus on the specific burden attributable to either pathogen, and thus on whether both pathogens are comparable public health priorities. Prioritization of vaccine candidates, given this uncertainty, is problematic, and there is a

Table 1
All-ages diarrheal mortality attributable to ETEC and *Shigella.*

Year represented	GBD 2010 [12]	GBD 2013 [10]	GBD 2015 [4]	FERG 2015 [14]
All-Cause Diarrheal Deaths (95% Uncertainty Interval)	1,445,800 (1,278,900–1,607,000)	1,264,100 (1,151,200– 1,383,200)	1,312,100 (1,233,600–1,391,300)	1,092,584 (892,999–1,374,238)
Number of ETEC deaths (95% Uncertainty Interval)	120,800 (95,700–147,600)	59,200 (44,200–77,700)	74,100 (29,900–137,900)	73,857 (53,851–103,026)
Number of *Shigella* deaths (95% Uncertainty Interval)	122,800 (97,400–149,600)	73,900 (58,900–93,800)	164,300 (85,000–278,700)	65,796 (46,317–97,036)

Table 2
Diarrheal mortality attributable to ETEC and *Shigella* among Children under Five (U5).

Study	CHERG/MCEE [5]	GBD 2013 [10]	GBD 2015 [4]
All-cause Diarrheal Deaths (95% Uncertainty Interval)	712,000 (491,000–1,049,000)	474,900 (398,100–545,000)	499,000 (447,000–558,000)
ETEC deaths (95% Uncertainty Interval)	42,000 (20,000–76,000)	23,100 (17,000–30,400)	23,600 (9600–44,300)
Shigella deaths (95% Uncertainty Interval)	28,000 (12,000–53,000)	33,400 (24,900–43,500)	54,900 (27,000–94,700)

danger of impeding or precluding the availability of an effective vaccine that may provide a significant public health benefit. Furthermore, as the long-term sequelae of ETEC and *Shigella* on morbidity, including child development, are becoming better appreciated, these effects may become a more significant criterion in future funding and procurement decision-making processes.

To address the uncertainty regarding ETEC and *Shigella* burden, the objective of this WHO consultation was to discuss the variability of the current mortality estimates; to examine the current state of knowledge with respect to the long-term indirect morbid effects of ETEC and *Shigella* infection; and to review the status of vaccine candidates in the pipeline. The intent was to set the stage for future discussions regarding product development priorities for development of vaccines against both ETEC and *Shigella*, in particular development consensus with respect to clinical and regulatory pathways, and WHO Preferred Product Characteristics for vaccines against both pathogens [20].

2. Status of the revised global burden of disease estimates for ETEC and *Shigella*

Both IHME and MCEE diarrheal estimates are currently undergoing revision, and interim analyses were presented at the consultation. Both updated estimates will incorporate molecular diagnostic methods to attribute etiology. The contribution of morbidity, both short and long term, will be included, and both studies adhere to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) [21,22].

A limitation of both IHME and MCEE analyses is that, in many settings, diarrhea diagnosis and case detection are not possible or are inadequate, therefore data from surrounding regions are extrapolated. An additional contributor to uncertainty and wide uncertainty intervals in these estimates is the geographic heterogeneity that exists for ETEC and *Shigella* disease burden (see Section 5).

2.1. MCEE 2017 updated systematic review of global causes of diarrheal disease mortality in children under-five

The 2013 CHERG/MCEE systematic review includes reported estimates of pathogen-specific mortality for the year 2011, using data from hospital inpatient studies as a proxy for etiologies [5]. The updated MCEE model will include studies from 1990 to 2014 and has revised the inclusion/exclusion criteria, as well as the modelling methodology. Estimates of pathogen-specific mortality and morbidity are included, with mortality estimates derived from hospital inpatient studies and morbidity estimates derived from hospital outpatient and community studies. Studies that were conducted prior to introduction of rotavirus vaccine are included.

Studies that did not separate inpatient data from those of outpatient or community data, assessed only one pathogen, utilized non-standard laboratory methods, or had less than a total of 100 cases total are excluded. Data obtained from the WHO Global Rotavirus Surveillance network (GRSN) are incorporated and adjusted to account for restriction of cases defined by acute watery diarrhea alone, and that excluded persistent and dysentery cases. The proportion of cases with unknown etiology is based on GEMS quantitative real-time PCR (qPCR) data from hospitalized patients. The mean age-adjusted pathogen-specific prevalence from inpatient studies is applied to the total 2015 under-five diarrhea mortality, pre-rotavirus vaccine adjustment, by WHO region.

2.2. IHME global burden of disease

Revised 2016 IHME diarrheal burden estimates are in progress and are attributed to thirteen etiologies including *Shigella* and ETEC. The estimates will include mortality as well as the Disability-adjusted life years (DALYs) to account for the impact of both short and long-term morbidity following enteric infections. DALYs are the sum of Years of Life Lost (YLLs) and Years Living with Disability (YLD) and are an overall metric of the burden of disease. Historically, GBD DALY estimations for diarrhea has been based on childhood deaths, however the updated DALYs will consider the impact across the full life course. The intent is to have an increased focus on more comprehensive assessments of the effects of diarrhea on long-term sequelae such as malnutrition, intellectual disability and growth faltering, but there is a significant lack of studies on these aspects. Earlier assessments of YLDs by IHME indicated that ETEC and *Shigella* are associated with a comparable amount of disability, and that they both rank among the top five causes of diarrheal associated YLDs worldwide [23].

3. Ongoing studies that will inform future disease burden estimates

3.1. GEMS and MAL-ED primary epidemiology studies

The original GEMS and MAL-ED studies used traditional methods of detection including culture based and immunological assays to attribute pathogen specific disease burden; however, recent iterations attributed etiology using molecular Taqman Array Card (TAC) qPCR assays.

GEMS was a population-based, multi-center case-control study in Africa and Asia that aimed to characterize the incidence, etiology, and outcome of the most life-threatening and disabling episodes of diarrhea among children <60 months of age. Children from selected LMIC sites were included if seeking medical care for moderate-to-severe diarrhea (MSD) according to pre-specified clinical criteria [16].

The MAL-ED study was a longitudinal 8-site birth cohort community based study at sites in South Asia, Africa, and Latin America. The goal of MAL-ED was to understand and measure the effects of malnutrition and its relationship with enteric infections among children under 2 years of age. Unlike the original GEMS study, MAL-ED assessed both milder and more severe cases of diarrhea through the collection of stool samples and anthropometric measurements [17].

The differences between these two studies has been discussed in a recent review [24].

3.1.1. Original GEMS and MAL-ED findings and outcomes

The 2013 publication of the original GEMS study found that over 50% of the attributable fraction of pathogens (PAF) that cause MSD were due to infection with rotavirus, *Cryptosporidium, Shigella*, ST-ETEC and enteric adenoviruses (serotypes 40 and 41). In analysis of all sites combined, ST-ETEC had the third highest attributable incidence in 0–11 month olds and was one of the few pathogens associated with an increased risk of death among cases in the 60 days following diagnosis (HR 1.9; 95% CI 0.99–3.5). *Shigella* had the fourth highest attributable incidence in this age group. The *Shigella* burden increased significantly in the second year of life across all 7 sites in the study while the attributable incidence due to ST-ETEC remained virtually unchanged. *Shigella* was found to have the highest attributable fraction in children 24–59 months of age. ST-ETEC was found to be associated with increased risk of death in infants aged 0–11 months and *Cryptosporidium* in toddlers aged 12–23 months.

There was variability in the point estimates of burden attributable to each pathogen across the study sites, but the confidence intervals were wide. The Mirzapur, Bangladesh site had a much higher burden of *Shigella* than other sites for the corresponding age groups, including another site in Bangladesh. This suggests extrapolation from specific sites or studies to reflect regional or national burden must be performed with caution.

In contrast, the MAL-ED study found that ETEC and *Shigella* were not among the top five enteropathogens that caused milder cases of diarrhea in the community during the first year of life. Norovirus GII, rotavirus, *Campylobacter* spp, astrovirus, and *Cryptosporidium* spp exhibited the highest PAF of diarrhea in the first year of life, whereas *Campylobacter* spp, norovirus GII, rotavirus, astrovirus and *Shigella* spp were highest in the second year of life.

Pathogen detection was common in non-diarrheal stools but the frequency was higher among children with diarrhea. Of the pathogens detected in cases associated with dysentery, dehydration or admission to hospital, rotavirus, *Campylobacter* and Norovirus GII were detected in the first year of life, and *Shigella*, rotavirus and ST-ETEC in the second year of life. Persistent diarrhea characterized 4.9% of diarrhea episodes in the first year of life and was associated with LT-ETEC, astrovirus, *Cryptosporidium*, ST-ETEC and *Shigella*, declining to 1.8% of episodes in the second year of life, primarily due to *Shigella* and astrovirus infection [17].

Similar to GEMS, there was heterogeneity in disease burden observed among the different sites, with *Shigella* disease burden increasing in older age groups. When calculating overall etiologic proportions, *Shigella* was the least common pathogen detected during the first year of life (<1.0%); whereas by the second year, its PAF quadrupled to make it the fifth most common pathogen (4.0%). ST- or LT-ETEC were not in the top five pathogens for either age group in the context of this community diarrhea study, but ST-ETEC was the sixth most common pathogen from 12 to 24 months of age. As in GEMS, ST-ETEC and *Shigella* were associated with more severe disease.

The differences between disease burden estimation for GEMS and MAL-ED highlight that ETEC and *Shigella* are predominant causes of MSD compared to milder cases of diarrhea.

3.1.2. Reanalysis of GEMS and MAL-ED samples using quantitative molecular diagnostic methods (qPCR) to identify causes of diarrhea, and other ongoing GEMS based analyses

A subset of both GEMS and MAL-ED stool samples were reanalyzed using TAC qPCR assays that provided a more sensitive diagnostic approach to detect pathogen specific etiology. The results for the qPCR reanalysis of GEMS samples confirmed ST-ETEC and *Shigella* as being among the top five pathogens [11]. Reanalysis of the MAL-ED data is ongoing and is expected to be completed by 2018.

GEMS characterized episodes of MSD to understand the illnesses that are most likely to lead to sequelae and death. In a one-year follow-up study designated GEMS-1A, episodes of less severe diarrhea (LSD) seeking care at the same health centers but not meeting criteria for MSD were also enrolled. Both MSD and LSD episodes occurred among hospitalized children and those seeking outpatient care. MAL-ED completed the spectrum of illness by identifying diarrhea episodes in the community by performing household surveillance. The episodes of LSD in GEMS and the community cases in MAL-ED are of substantial public health importance because of their high prevalence and the observation that, even though the diarrheal illness and their sequelae may be milder, these episodes of LSD are associated with poor growth, impaired cognitive development, environmental enteropathy, as well as mortality [25,26]. As suggested by the MAL-ED studies, the pathogens that cause community diarrhea are likely to show a different pathogen hierarchy to that associated with MSD.

3.2. (Rotavirus) Vaccine Impact on Diarrhea in Africa (VIDA)

The VIDA study aims to assess the effects of rotavirus vaccination at three GEMS sites in The Gambia, Mali, and Kenya, where rotavirus vaccine has been introduced. The study seeks to analyze the epidemiologic impact of rotavirus vaccine introduction by comparing data collected pre- (i.e. during GEMS) and post-introduction (i.e. VIDA), to assess the impact on overall enteric disease incidence, etiologic distribution and adverse clinical consequences of MSD (for example persistent diarrhea, linear growth). Whereas in GEMs TAC qPCR was performed on a subset of cases and controls, in VIDA, qPCR is being performed on all cases and one control per case. The data from the VIDA study will improve our understanding of the causes, burden, and outcomes of MSD among children U5 and ensure that diarrhea treatment and prevention strategies are relevant and appropriate to the causes and consequences of diarrheal diseases in the coming decades.

4. Expanded global surveillance of ETEC and *Shigella*

Despite major improvements in the understanding of diarrheal etiology among hospitalized cases U5, gaps remain in estimates of the pathogen specific disease burden attribution and distribution. More information is needed to demonstrate vaccine impact and inform policy-making.

To address this need, a subset of surveillance sites that are part of the WHO Global Rotavirus Surveillance Network have been investigating the use of the qPCR Taqman array card to expand surveillance across a range of common enteric pathogens, including ETEC and *Shigella;* this investigation is referred to as Global Pediatric Diarrheal Surveillance (GPDS). A significant limitation of the epidemiological data derived from the GRSN to date has been that the current case definition for MSD did not include bloody or persistent diarrhea, which are common symptoms of *Shigella* and ETEC infection. For this reason, the number of ETEC and *Shigella* cases detected are considered an under-estimation, particularly for *Shigella*. Therefore, the MSD case definition for GPDS and other future surveillance studies will be modified to include bloody or persistent diarrhea to assess more accurately *Shigella* and ETEC disease burden. Other limitations include the lack of outpatient surveillance, and post-visit follow-up. As demonstrated in GEMS, many health facilities in LMICs do not hospitalize children with MSD, so the burden of disease will be underestimated. Moreover, children with MSD were 8.5 times as likely as their matched controls to die during the 90 days after an episode of MSD, but only 26% of these deaths occurred during their enrollment visit. Without outpatient follow-up, these deaths will be missed.

Moreover, the remit of GPDS post-introduction of rotavirus vaccine is to assess the longitudinal changes in disease burden and to characterize rotavirus vaccine impact in regions of vaccine introduction. This includes, for example, documenting decreases in pediatric diarrhea and rotavirus disease, assessing rotavirus genotype changes, and identifying shifts in etiology of pediatric diarrhea. The data generated from these studies will help to inform the product development strategies with respect to the optimal vaccine formulations (component strains or antigens) and schedules. Current data from the GRSN have included 840 specimens from hospitalized, acute watery diarrhea from 16 countries. *Shigella* and ETEC were both listed among the top five pathogens [27].

WHO regions where GPDS surveillance sites are located include AFRO, AMRO/PAHO, SEARO, WPRO, and EURO. High burden EMRO countries were under-represented in the network due to a lack of resources to conduct effectively this surveillance in politically unstable environments and concerns about polio containment in countries with recent or current polio transmission. Various key country data gaps include Afghanistan, Sudan, and Somalia. Nigeria and Pakistan may be included; however, they were not confirmed at the time of the consultation due to concerns that testing stool for such surveillance could potentially interfere with polio containment. Current countries within GPDS include non-Gavi eligible and/or self-procuring vaccine countries. It was noted that use of tertiary or academic hospitals as surveillance sites is most practical and is common among GRSN sites, but these surveillance sites may not provide data that reflect etiologic distribution in rural areas and for non-rotavirus pathogens such as *Shigella* and ETEC. Future sites for GPDS should consider more primary or secondary district hospitals to better represent the etiology within geographically remote regions.

The goal of the first phase of GPDS expansion is to provide broader estimates of diarrheal etiology from 2017 to 2019. Future activities of this surveillance network could include greater emphasis on distinguishing between MSD and LSD cases, as well as assessment of associated case morbidity.

5. Heterogeneity in ETEC and *Shigella* disease burden, and considerations for vaccine cost- effectiveness

Heterogeneity in disease risk and burden has important implications for vaccine implementation strategy, effectiveness and impact. While decreases in diarrheal disease burden are often due to factors such as introduction of rotavirus vaccine, increased access to clean water, sanitation and health care, the variation in geography and socioeconomic status means that these interventions are not always accessible to all [28]. Consequently, substantial heterogeneity in ETEC and *Shigella* disease burden estimates exist both between and within countries; however, the confidence intervals are wide. Characterization of these differences will be critical to informing the cost-effectiveness of potential vaccine introduction strategies.

6. Long term morbidity effects of ETEC and *Shigella* infection

In addition to the mortality burden of diarrhea in LMICs, exposure to enteric pathogens is associated with various other chronic morbidity effects, including the disorder known as environmental enteric dysfunction (EED) [29]. Efforts are ongoing to elucidate and characterize the biological mechanisms and potential long-term consequences of clinical, as well as subclinical, i.e. asymptomatic, enteric infection, as these have a significant, quantifiable contribution to the burden of ETEC and *Shigella* disease that is currently not represented in economic analyses of potential vaccine impact.

The hypothesized health burden of frequent diarrhea episodes, recently comprehensively reviewed by Guerrant et al. [30], includes increases in stunting, impaired growth, impeded cognitive growth, and an increased risk of developing chronic illness later in life [31]. Potential effects are expressed in terms of height/length for age z score (HAZ)-drop (reduction in height for age scores), and COG-hit (cognitive growth impairment) during the first two years of life. MET-syn refers to the range of metabolic syndromes that manifest in various chronic metabolic and cardiovascular conditions. Data from five longitudinal prospective cohort studies from Brazil, Guatemala, India, the Philippines, and South Africa showed that indices of maternal and child under-nutrition (maternal height, birth weight, intrauterine growth restriction, and weight, height, and body-mass index at 2 years according to the new WHO growth standards) were related to adult outcomes, including height, reduced attainment at school, reduced income or assets, offspring birth weight, body-mass index, glucose concentrations, and blood pressure. Victora et al. found that HAZ at 2 years (HAZ-2) was the best predictor of human capital [32]. Chronic diseases are especially common in undernourished children who experience rapid weight gain after infancy. Evaluation of these disorders following repeated enteric pathogen exposure would help define the magnitude, causes and costs (in terms of DALYs), and provide additional data with respect to beneficial health, educational, and economic outcomes of preventing or reducing infection in infancy. While these longitudinal studies are crucial to defining the broader cost-effectiveness for ETEC and *Shigella* vaccines, they are challenging to undertake due to competing priorities in a resource-constrained field, the significant costs of these studies, and retention of participants through their prolonged duration.

There are numerous publications that suggest early childhood diarrhea, particularly prolonged and/or repeated episodes, is associated with growth faltering [26,33]. A range of fecal biomarkers has been found to be associated between intestinal inflammation and linear growth failure, namely neopterin [NEO], alpha-antitrypsin [AAT], and myeloperoxidase [MPO]), for which enzyme-linked immunosorbent assays are now commercially available [34]. When these metrics are factored together to form a disease activity score, children with the highest score grew 1.08 cm less than children with the lowest score over the 6-month period following the tests, after controlling for the incidence of diarrheal disease. These assays could delineate those at risk of linear growth failure and may be used for the improved assessments of interventions, such as vaccines, so that their contributions to further growth optimization during early childhood can be better understood.

Both ST- and LT-ETEC-LT were associated with a more significant drop in HAZ scores. While LT-ETEC is not often considered to be as pathogenic as ETEC-ST, LT-ETEC's possible association with long-term impairments indicates that subclinical or less severe infections could have important long-term effects on health [26].

7. Cost-effectiveness and modelling vaccine impact of ETEC and *Shigella* vaccines

A cost-effectiveness analysis of a combination vaccine against ETEC and *Shigella*, that includes the impact on ETEC and *Shigella* induced stunting and the subsequent risk of mortality from other childhood infectious diseases, is in progress, and preliminary results were presented at the consultation. The model includes 96 LMICs that represented a range of economic, geographic and mortality settings across the global WHO regions. Model inputs included an assumed vaccine efficacy of 60% with 3 doses per regimen, and a cost of $5/dose. The mortality estimates were based on a mid-point estimate for each country using the 2013 estimates from MCEE and IHME. Due the heterogeneity of ETEC and *Shigella* disease, the cost-effectiveness of the vaccine was found to vary across countries. If the vaccine is introduced by strategically prioritizing areas where vaccination is most impactful, i.e. those countries with an incremental cost-effectiveness ratio of less than 3 times the country's gross domestic product (GDP), over 90% of deaths are predicted to be averted.

Assessment of the long term burden using estimated HAZ shift as a proxy for years of education lost and impact on lifetime earnings, the model predicts that the average burden of ETEC and *Shigella* is $64 per child, with an annual burden of $7 billion and 1.3 million child school years lost as a result of infections. Assuming the vaccine is introduced in 2025, it would result in averted stunting that could lead to $31 billion in future earnings gained over 10 years, compared to $17 billion in net introduction costs. Even if the shifts in HAZ attributable to ETEC and *Shigella* diarrhea were half of those used in the model, costs of introduction would still be offset with the benefits of future earnings. A limitation of this model is that the effects of ETEC vaccination are not separated out from those of *Shigella*; therefore, it is difficult to determine the relative contributions of the two pathogens.

As mentioned above, cost-effectiveness of combined ETEC and *Shigella* versus standalone ETEC or *Shigella* vaccine formulations will likely differ based on sub-regional or sub-national etiological differences, as well as the timeline to vaccine availability (licensure). A risk modelling approach is under development to assess the potential impact of ETEC and *Shigella* burden on stunting, and how disease heterogeneity could adversely affect vaccine impact and cost effectiveness.

8. The current vaccine candidate pipeline, and product development strategy

Several promising vaccine candidates are in clinical development against both *Shigella* and ETEC (Table 3) [35,36]. Some may be amenable to presentation as a combination vaccine, i.e. 2 or more vaccines that have been combined by the manufacturer or supplied as vaccine components that are formulated to be combined immediately before administration [37]. Although not specifically discussed at this consultation, the considerations and product development challenges for developing combination vaccines have been reviewed recently [38–40]. The 'ideal' attributes for an ETEC and/or *Shigella* vaccine were proposed at this meeting, and include administration to infants less than 6 months of age, within the Expanded Programme of Immunization (EPI) schedule, use of a single, self-contained, orally administered dose in less than 2 mL of liquid. Given the increase in *Shigella* incidence after 12 months of age, the duration of the protective immunological response should persist for at least 2 years after the vaccine is administered in the first few weeks of life. Depending on the immune response of the vaccine, it may be optimal to administer *Shigella* vaccines later in infancy, but before the 12–24 month old period of greatest susceptibility.

ETEC strains achieve antigenic diversity through the expression of multiple colonization and surface factor antigens and toxins, therefore, an efficacious vaccine will likely need to consist of multiple components or strains. Of the 25 colonization factors identified to date, some are more prevalent than others, and may offer some degree of cross protection; a vaccine containing CFA/1, CS3, CS5 and CS6 is predicted to offer approximately 70–80% coverage across all circulating ETEC strains [41,42]. Addition of an LT-like toxoid in the form of the adjuvant double mutant LT (dmLT) may increase protection against diarrhea, reduce colonization, and facilitate dose sparing (and therefore lower volumes) particularly in infants and young children. With respect to *Shigella*, there are 4 major species and 50 different serotypes, but a combination of *Shigella sonnei* and *Shigella flexneri* serotypes 2a, 3a and 6 is predicted to offer coverage of approximately 88% of isolates [43]. Therefore, development of individual ETEC and *Shigella* vaccines will themselves need to be composed of multivalent combinations. A combination ETEC and *Shigella* vaccine will require all of these components to be compatible, both with respect to stability and immunogenicity, and for the cost of procurement and delivery to be affordable, which present significant additional challenges beyond for those faced by stand-alone vaccines. The alternative strategy is the hybrid approach, in which the backbone of one pathogen is genetically manipulated to express antigenic components of the other. Ideally ETEC and *Shigella* vaccines will be orally administered to reduce the number of parenteral administrations within the already heavily crowded EPI schedule, and to ease the burden on healthcare workers.

Table 3
Overview of ETEC and *Shigella* vaccine candidates currently in development, and their development stage. The shades indicate administration route: green indicates oral, blue indicates parenteral and purple indicates intranasal. The **bold** indicates ETEC and *Shigella* candidates that may be compatible for combination. The *italics* indicate chimeric vector based platforms that present both ETEC and *Shigella* antigens in a single construct. *Indicates discontinued.

Platform	ETEC					Shigella				
	Preclinical	Phase I	CHIM	Phase II	Phase IIb	Preclinical	Phase I	CHIM	Phase II	Phase IIb
Inactivated whole cell vaccines		**ETVAX (OEV-121) EudraCT No:2011-003228-11**		**ETVAX (OEV-122) NCT02531802**	**ETVAX (OEV-123) EudraCT No: 2016-002690-35**		**Sf2aWC (VAC 001) NCT01509846**	**Sf2aWC + dmLT NCT03038243 (funding pending)**		
Live-attenuated whole cell vaccines		ACE527-101* (frozen) NCT00901654	ACE527-102* (frozen) NCT01060748				WRSS1 (VirG series) NCT01813071 (VAC 008) - adults/children NCT02934178 (VAC 049) - toddlers	WRSS1 (VirG series) NCT01080716		
			ACE527* (VAC 006 lyophilized) NCT01739231				WRSS2/WRSS3 (VirG series) NCT01336699			
Chimeric vector	ZH9 typhoid/ETEC					Ty21a/Shigella				
	GUA Shigella mutants					*GUA Shigella mutants*				
	ShigTEC					*ShigTEC*				
Recombinant/sub-unit based	LT/ST fusion constructs	CfaE/CfaE-LTB Chimera + mLT (TCI vs ID) NCT01644565	CfaE +mLT (ID) NCT01922856				Bacterially expressed glycoconjugate NCT02388009	Bacterially expressed glycoconjugate NCT02646371		
	multiepitope fusion antigen (MEFA)						InvaplexAR NCT02445963			
							SF2a-TT15 conjugate NCT02797236			
Other							Generalised Modules for membrane molecules (GMMA) - France NCT03089879			
							Generalised Modules for membrane molecules (GMMA) - Kenya NCT02676895			

8.1. ETEC vaccine candidates and combination with other enteric pathogens

8.1.1. Oral administration

Most ETEC vaccine candidates are based on either oral cellular (live attenuated or killed whole cells) or parenteral subunit based approaches and are designed to elicit anti-colonization and anti-toxin responses. The most advanced oral ETEC vaccine candidate (ETVAX, Scandinavian BioPharma) is a tetravalent, inactivated whole-cell ETEC vaccine containing dmLT [44]. This candidate is currently in a phase 1/2 age descending, dose finding safety and immunogenicity study in Bangladesh (NCT02531802), as well as a phase IIb study in travelers (EudraCT-2016-002690-35). Similarly, the candidate ACE527 is a combination containing dmLT, but based on three live attenuated strains that express CS/CFA antigens [45,46]. Although ACE527 demonstrated protective efficacy in an adult human challenge study, further clinical studies will require significant process development, which at the time of writing, is not in place. There are other oral ETEC candidates in preclinical development, but as hybrid approaches with other enteric pathogens, including *Shigella* and typhoid (Prokarium).

8.1.2. Parenteral administration

The most advanced parenteral approach uses the relatively conserved fimbrial tip adhesins (FTA) that facilitate binding of ETEC *in vivo* (PATH, NMRC, Sanofi, IDRI). Proof of principle for this approach was demonstrated in a murine and non-human primate challenge study [47,48], and efforts are ongoing to further optimize the construct and formulation for future studies. Kansas University has a preclinical parenteral candidate in development based on the Multi-epitope Fusion Antigen (MEFA) approach that expresses the dominant epitopes of CFAs on ETEC as a single antigen [49,50].

8.2. Shigella vaccine candidates and combination with other enteric pathogens

Broadly speaking, *Shigella* vaccine candidates are either directed against serotype specific *Shigella* lipopolysaccharide (LPS)-associated O—antigen or conserved antigens such as the invasion plasmid antigens (Ipas). The drawback of the O-antigen approach is that a multivalent strategy will be needed, whereas the conserved antigens are generally less immunogenic, require the addition of adjuvants, and their ability to confer protection against illness remains unconfirmed.

8.2.1. Oral administration

A trivalent killed whole cell (TSWC) combination candidate composed of *S. flexneri 2a, S. flexneri 3a*, and *S. sonnei*, is expected to offer 80% coverage against circulating serotypes. Two components of this trivalent vaccine concept have been shown to be safe and immunogenic in a Phase I study [51,52] (NCT03038243). Other whole cell candidates are based on live cells that have been attenuated by genetic manipulation to improve their safety, whilst maintaining a favorable immunogenicity profile. These include the Δ*virG*-based mutants (WRAIR) and the Δ*guaBA*-based mutants (University of Maryland). The Δ*virG* -based *S. sonnei* component (known as WRSs1) of an intended multivalent vaccine is currently in clinical phase 2a studies in infants and young children in Bangladesh (NCT01813071 and NCT02934178).

Subunit based approaches for parenteral delivery of *Shigella* vaccines are also in development, the most advanced of which is a recombinant glycoconjugate that is currently in a phase II human challenge study (NCT02646371). The Institute Pasteur is also developing a glycoconjugate candidate consisting of synthetically produced *S. flexneri* oligosachharide mimics that are conjugated to carriers proteins, which are currently in phase I studies (NCT02797236). Other approaches include using outer membrane vesicles (OMVs) of *Shigella*, known as Generalized Modules for Membrane Antigens (GMMA). A tetravalent GMMA formulation (*S. sonnei, S. flexneri* 2a, 3a and 6) has been shown to be immunogenic in mice, and *S. sonnei* prototype safety and immunogenicity in phase 1 has been demonstrated (NCT02676895 and NCT03089879). A descending age and human challenge trial is planned to commence within the next year.

The most advanced conserved antigen approach focuses on targeting the *Shigella* invasin complex (Invaplex). The second-generation candidates combine serotype-specific LPS in a macromolecular complex with broadly conserved Ipa proteins and have been shown to be safe and immunogenic in a phase I study (NCT02445963). Further optimization of this candidate to generate a multivalent construct is ongoing. Several other sub-unit based candidates that are targeted for parenteral administration are in development.

The MEFA approach is also amenable to the oral route if expressed from a vector such as Ty21a, as in the approach taken by Protein Potential.

The pipeline of active ETEC and *Shigella* vaccine development is shown in Table 3. Considering the relative stages of development, and the potential compatibilities of the ETEC and *Shigella* components, combination of the ETVAX and TSWC killed whole cell candidates provide the earliest opportunity for licensure of an ETEC-*Shigella* combination vaccine, either as a single co-formulation, or as co-packaged vaccines that are administered separately but concurrently. However, there is no precedence for regulatory approval of combinations of novel vaccines without prior licensure of one of the vaccines (that would itself be a combination). Neither ETEC nor *Shigella* have an established correlate of protection, and neither has a candidate that has demonstrated field efficacy to serve as a benchmark against which to measure potential immunological interference when the other is co-administered. A possible strategy may be to demonstrate efficacy against one pathogen, then test the efficacy of the combination against the second pathogen, with an immuno-bridge to the previously tested pathogen to evaluate potential immunological interference of the combination [38]. Controlled human challenge models for *Shigella* and ETEC are well-developed and might be useful in this regard. Alternatively, the *Shigella* and ETEC vaccines could be licensed separately, based on field efficacy and/or challenge trials, then combined and use immunogenicity to demonstrate non-interference. Consideration of the product development pipeline suggests that this strategy may de-risk the combination approach as it offers greater opportunity for future combination (the excipients of whole cell killed vaccine are generally considered unlikely to be compatible with subunit or live attenuated vaccine candidates), both between ETEC and *Shigella*, but also with other enteric vaccines that are in development. It will also offer greater flexibility in terms of optimal administration age and sub-national implementation.

9. Positioning the value proposition for ETEC and *Shigella* vaccines

The value proposition of a vaccine candidate defines its epidemiologic, economic, market, policy, financing, delivery and regulatory environments to guide investment in that product. Value propositions seek to identify the major stakeholders and beneficiaries, who may value the product differently, and articulate how the envisaged product will address their unmet need, as well as identify gaps in evidence to justify the product's uptake. In this way, value propositions inform candidate prioritization, as well as guide product development strategy and investment decision making. For this reason, value proposition evaluations are important to undertake early in product development to help shape target product profiles and de-risk expenditure.

One of the fundamental elements that will inform the ETEC and *Shigella* vaccine value proposition is a robust assessment of the current, and future, mortality and morbidity-related economic burden of disease. The DALYs associated with stunting contribute a substantial amount of the underlying disease burden for these pathogens, and can also be seen in the number of annual deaths predicted due to other infectious diseases because of ETEC and *Shigella* associated stunting. In addition, the long-term consequences of repeated ETEC and *Shigella* infections increase the risk of death in infants and young children from other, unrelated infectious diseases, such as pneumonia and malaria. It also impact their cognitive development and increases their risk of chronic diseases. For this reason, it is imperative to capture the full burden of ETEC and *Shigella*. To date, burden estimates have not included estimates of DALYs specifically assessing long-term sequelae such as stunting, malnutrition, and cognitive impairment; the 2016 iterations will be the first to do so. Both ETEC and *Shigella* also cause significant acute illness in travelers and there is increasing evidence that they may also contribute to a significant number of functional bowel disorders and other long-term chronic sequelae that can affect 10–14% travelers after their recovery from their initial clinical episode [53]. A recent systematic review of 51 publications suggests that ETEC was detected in 30.4% of overall traveler's diarrhea cases, with the highest rates in travelers to Latin America/Caribbean, Africa, South Asia, and Southeast Asia [2,51]. *Shigella* has also been identified as a leading cause of persistent diarrhea (≥14 days) in residents, expatriates of developing countries, or travelers to these regions [54]. In a study performed in the United States military where ETEC and *Shigella* were identified as the cause for 22% (99% CI 16.9–27.5) and 6.6% (99% CI 3.4–9.7) of diarrhea, respectively [2]. Although less frequent, *Shigella* has been shown to produce a particularly debilitating illness in these populations. Both of the traveler and military populations represent substantial market segments that support the value proposition for ETEC and *Shigella* vaccines; however, the target product profiles for vaccines that are developed for travelers and military need also consider the programmatic requirements for a vaccine to be suitable for use in LMICs, in order for these vaccines to have global reach and impact on reducing disease and transmission.

Both *Shigella* and ETEC have developed high levels of antibiotic resistance. *Shigella* has been identified as a community acquired infection of great concern because of its high level of antibiotic resistance, and it has been identified as a priority pathogen for assessment in WHO's Global anti-microbial resistance (AMR) Surveillance System [55]. Antibiotic resistance against these enteric pathogens is likely to continue to rise as a result of inappropriate antibiotic use, and has prompted a safety warning related to ciprofloxacin use. The reduced capacity to control these pathogens with antibiotics further emphasizes the need for effective enteric vaccine.

10. Conclusions and recommendations

Diarrhea remains a leading cause of global morbidity and mortality, with the burden highest in the world's poorest children. Despite substantial reductions in mortality as a result of rotavirus vaccine introduction, improved diarrhea treatment, and better sanitation and hygiene, diarrhea still causes half a million deaths annually in under five year olds. ETEC and *Shigella* are among the top five pathogens that cause diarrheal mortality in this age group, and they also cause significant burden across all ages. However, the estimates of pathogen-specific mortality vary, and there is reported heterogeneity in ETEC and *Shigella* burden between, and within, countries. Importantly, although various studies indicate substantial and consequential long-term indirect effects of *Shigella* and ETEC infection and disease, the impact of long-term morbidity, in particular stunting, malnutrition, and cognitive effects after infection is not fully quantified. Furthermore, the persistent burden of these pathogens underscores the critical need for new prevention strategies, especially because Water, Sanitation and Hygiene (WASH) and antibiotic treatment control strategies continue to be challenging to implement in low resource settings, particularly in the context of rising global antibiotic resistance. Since control of antibiotic resistance is a global priority [56], the role of vaccines for ETEC and *Shigella* in reducing the use of antibiotics, and the amount of antibiotic resistant bacteria circulating in populations worldwide, should be considered in tackling AMR globally.

Comprehensive and robust disease burden estimates are needed, not only to inform product development investments, but also to be able to initially model and eventually demonstrate vaccine impact and cost-effectiveness. Additionally, an assessment of differences in morbidity and mortality between antimicrobial resistant versus sensitive strains is needed to evaluate the potential impact of these vaccines if they are able to protect against AMR strains This broader assessment of burden is pivotal for guiding evidence-based policy decision making and optimizing vaccine introduction. For this reason, WHO, through its advisory committee PDVAC and the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC), intends to establish an independent working group to collaborate with the developers of the two most comprehensive ETEC and *Shigella* global disease burden estimates, namely IHME and MCEE. The objective will be to understand better their uncertainties and limitations of the models and the data, and to lay the foundation for eventual policy consideration.

Surveillance and accurate determination of etiology is fundamental to improving disease burden estimation. Several epidemiology and etiology studies are ongoing that will improve future estimates; however, parallel efforts are needed to characterize the accuracy and limitations of current diagnostics, including qPCR-based assays, and to ensure that detection methods and procedures are standardized across sites, as well suitable for use in remote field and clinic based settings. Assessment of antibiotic use and resistance in both clinical and surveillance studies should be prioritized to better characterize the emergence of antibiotic resistance to these pathogens, and proactively manage the most effective treatment options.

Despite the identification of both ETEC and *Shigella* as leading causes of diarrheal mortality, several participants at this meeting reported that, at the healthcare worker level, there is a lack of association of diarrheal disease with specific pathogens, including ETEC and Shigella. Efforts are needed to raise awareness of these two pathogens as major causes of devastating of disease in affected countries, as well as the reduced effectiveness of antibiotic treatment because of increasing resistance. This will empower countries to advocate for development of vaccines that will address the need in their specific contexts, and help to drive the demand for these cost-effective interventions.

In addition to the urgent need for ETEC and *Shigella* vaccines to address the global public health need, these pathogens cause significant burden to travelers and the military. This potential market has driven much of the product development to date, but if these candidates are intended for global use, their programmatic suitability (for example route of administration, dose volume) and fit (number of doses, vaccination schedule) for immunization of infants and children in LMICs must be considered early in development.

Given the variation in the currently available disease burden estimates for ETEC and *Shigella*, and the expectation that these will

Table 4
List of consultation participants.

Name	Affiliation	Location
Presenters		
George Armah	University of Ghana	Accra, Ghana
Robert Black	Johns Hopkins University	Baltimore, USA
Roma Chilengi	Centre for Infectious Disease Research in Zambia	Lusaka, Zambia
Dick Guerrant	University of Virginia	Charlottesville, USA
Eric Houpt	University of Virginia	Charlottesville, USA
Wilson Mok	Gavi, the Vaccine Alliance	Geneva, Switzerland
Ibrahim Khalil	University of Washington	Seattle, USA
Carl Kirkwood	Bill and Melinda Gates Foundation	Seattle, USA
Karen Kotloff	University of Maryland	Baltimore, USA
Laura Lamberti	Bill and Melinda Gates Foundation	Seattle, USA
Farzana Muhib	PATH	Seattle, USA
Carmem Pessoa da Silva	Anti-microbial resistance, World Heath Organization	Geneva, Switzerland
Richard Rheingans	Appalachian State University	Boone, USA
Mark Riddle	U.S. Naval Medical Research Center	Silver Spring, USA
Richard Walker	PATH	Seattle, USA
Participants		
Annaliesa Anderson	Pfizer Vaccine Research and Development	Pearl River, USA
Shahida Baqar	National Institutes of Health	Rockville, USA
Lou Bourgeois	Johns Hopkins University	Baltimore, USA
Nils Carlin	Scandinavian Biopharma	Solna, Sweden
Fred Cassels	PATH	Seattle, USA
Sophie Druelles	Sanofi Pasteur	Lyon, France
Karine Goraj	GlaxoSmithKline	Siena, Italy
Lars Gredsted	Wellcome Trust	London, UK
Michelle Helinski	European & Developing Countries Clinical Trials Partnership	Hague, The Netherlands
Divya Hosangadi	Johns Hopkins University	Baltimore, USA
Varsha Jain	Bill and Melinda Gates Foundation	Seattle, USA
Mark Jit	London School of Tropical Medicine and Hygiene	London, UK
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Carl Kirkwood	Bill and Melinda Gates Foundation	Seattle, USA
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continue to shift as detection and modelling methodologies are further optimized, the conclusion from this consultation was that it is premature to deprioritize either pathogen at this time. Equally, preferential focus on development of a combination ETEC/*Shigella* vaccine approach will likely delay availability of ETEC and *Shigella* vaccines relative to the stand-alone approach. The candidates in the current pipeline may not be compatible, their product development timelines may not converge to support combination, or there may be opportunities to develop combinations with other, more suitable enteric vaccines, such rotavirus or norovirus. For these reasons, WHO will embark on developing preferred product characteristics (PPCs) for both ETEC and *Shigella* vaccines as stand-alone products [20]. [N.B. PPCs describe WHO's preferences for use of classes of vaccines, and help to shape subsequent product-specific target product profiles (TPPs)] [20].

The final recommendation from this consultation was to develop clear value propositions for ETEC and *Shigella* vaccines, incorporating the economic benefit that a vaccine could have though reduction of mortality and the long term and indirect morbidity effects, as well as reduction the use of antibiotics for treatment. Value propositions for ETEC and *Shigella* vaccines are particularly important as GAVI, the Vaccine Alliance, enters its next Vaccine Investment Strategy cycle, and is seeking to understand the potential availability and impact of vaccines that may emerge from the pipeline in the next 5–10 year period.

Acknowledgements

Sincere thanks to Dr. Louis Bourgeois and Dr. Dick Walker for their advice while planning this consultation. We are very grateful to all who presented and participated in this meeting for their expert contribution.

We gratefully acknowledge funding from the Bill & Melinda Gates Foundation to support the consultation reported here (OPP1135836). The views, findings, and conclusions contained within are those of the authors and should not be construed to represent the positions or policies of the Bill & Melinda Gates Foundation, the US Department of Defense, the US National Institutes of Health, or the World Health Organization. We are very grateful to all participants at the meeting (Table 4).

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