2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 3: Full Value of Vaccine Assessment (FVVA) for Shigella vaccines
18 May 2020

Participants:

PDVAC: Isabelle Bekeredjian-Ding (for Klaus Cichutek), Sinead Delany-Moretlwe, Barney Graham, Gagandeep (Cherry) Kang, Ruth Karron, David Kaslow (Chair), Jerome Kim, Claudio Lanata, Shabir Mahdi, Yiming Shao, Peter Smith, Marian Wentworth, Beno Nyam Yakubu; Mark Papania

Apologies: Bernard Fritzell

WHO: Birgitte Giersing, Mateusz Hasso-Agopsowicz, Erin Sparrow, Ibrahim Khalil, Philip Lambach

Chair of SAGE: Alejandro Cravioto

Observers and non-member participants: Louis Bourgeois (PATH), William Hausdorff (PATH), Jens Kieckbusch (Wellcome), Cal MacLennan (BMGF), Deepali Patel (Gavi), Evan Simpson (PATH), Duncan Steele (BMGF, Carolyn Deal (NIAID), Chad Porter (NMRC), Farzana Muhib (PATH), Francesca Micoli (GSK), James Platts-Mills (University of Virginia), Jeroen Geurtsen (Janssen), Karen Kotloff (University of Maryland), Mark Jit (LSHTM), Patty Pavlinac (University of Washington), Sally Nicholas (Wellcome), Suzanne Scheele (PATH).

Executive Summary

Rationale for topic: In 2016, PDVAC prioritised *Shigella* vaccines, undertaking to facilitate and accelerate their product development and pathway to policy. PDVAC/WHO IVB is also developing the concept of the Full Value of Vaccine Assessment (FVVA). PATH have identified the major themes to inform a FVVA for *Shigella* vaccines, and WHO IVB would like to collaborate on and support this effort. This session is to discuss the critical questions that could inform the assessment from the PDVAC perspective, the relative importance of those critical questions, and to identify gaps or other questions that should also be considered.

PDVAC Conclusions and Recommendations:

- *The Shigella FVVA should include a full assessment of data and analysis related to the impact of stunting as a consequence of Shigella infection, and the long-term effects of stunting.*
- *The field needs to look for opportunities to examine the effect of stunting in clinical studies; probe studies may inform the optimal metrics to be evaluated, and improve limitations of cost-effectiveness and vaccine impact models, and practically, how data may be collected.*
- *Undertaking a macro-economic analysis of Shigella impact will be challenging but is expected to be useful to inform decision makers at the country level with respect to*

Shigella vaccine introduction, in the context of 1) other interventions to prevent and/or treat Shigellosis, and 2) use of other vaccines.

- *For AMR, it would be important to estimate the ability of a Shigella vaccine to 1) reduce the prevalence of AMR strains of Shigella; and 2) reduce the Shigella or diarrhoea-associated antibiotic use or consumption. Measuring vaccine impact on the prevalence of AMR requires assessment over the long-term and is unlikely to be feasible during vaccine development. Instead, the vaccine impact on the reduction of Shigella or diarhoea-associated antibiotic use or consumption (through estimating the number of vaccine averted cases that would otherwise be treated with antibiotics) could be a reasonable proxy to estimate the vaccine impact on AMR. WHO is developing a framework to measure the impact of vaccines on AMR, and will estimate the vaccine-associated reduction in antibiotic use and consumption associated with Shigella infections. The vaccine impact on AMR strains of Shigella should be assessed and monitored post licensure.*
- *The FVVA for stand-alone Shigella vaccines needs to be undertaken initially, to determine if a stand-alone has a compelling value proposition but also to be able to evaluate how the value proposition would change incrementally in the context of a combination vaccine. It is anticipated that the cost-effectiveness of a Shigella vaccine would increase when included as part of a combination vaccine. Determining which combination vaccines would have favorable value propositions is anticipated to incentivize development of Shigella-containing vaccine.*
- *The FVVA is not a static document; it is a compilation of existing evidence but also a dynamic process of stakeholder engagement and alignment around the data, gaps and strategic directions. Consolidation of this stakeholder engagement and communication needs to occur throughout vaccine development and subsequently lead to further refinement of the FVVA.*
- *The health-economic lens may be different to the public health decision-making priorities and criteria – global stakeholders and vaccine developers need to understand the priority criteria of countries to inform the FVVA and evidence generation approach. PDVAC strongly advocates for the use of the FVVA approach to build awareness and early global stakeholder alignment.*
- *The decision-making contexts and drivers within LMICs differ and are dynamic. MALED and GEMS are already 10 years old; will the data from these two studies still be relevant in decision-making a decade from now when Shigella-containing vaccines may be ready for introduction? Country and regional engagement are key to understanding current priorities and how these priorities have changed over time.*

***Post meeting comment**: The FVVA should consider if the cost-effectiveness of Shigella vaccines, alone or in combination, could be improved by targeting the most at-risk populations for stunting and other adverse outcomes of Shigellosis.*

1. Context of the meeting

A vaccine candidate will encounter several inter-dependent hurdles along the pathway to use and impact. These have been characterized recently by Piot et al (2019). The phases of product development, licensure, policy recommendation, financing and procurement exist along a continuum, and early engagement, alignment, and co-ordination of the respective stakeholders could be enhanced through information and incentives. The Full Vaccine of Vaccines Assessment (FVVA) is a concept that describes the global value of a vaccine and aims to articulate its full direct and indirect effects. The intent of a FVVA is to support decision-making across the continuum of vaccine development and uptake, with a line-of-sight to sustainable socio-economic and public health impact.

Several *Shigella* vaccine candidates are currently in Phase II trials. At least one will require evaluation in a costly Phase III field efficacy study to support licensure in the priority target population of infants and children below 5 years of age, in low- and middle-countries (LMICs). Considering the number of candidates that are in late-stage development across various diseases, the relative 'value' of vaccines is becoming increasingly crucial to quantify, and to inform priority setting for investment, policy, and introduction decisions. This need is particularly pertinent for *Shigella* vaccines, given the reduction in mortality from *Shigella* infections over the last decade (although the morbidity burden remains significant and poorly characterised) and its heterogenous epidemiology. This means that *Shigella* vaccine introduction may be most cost-effective at a subnational level, or if used in combination with other enteric vaccines. In addition, there is evidence of increasing antimicrobial resistance (AMR) to *Shigella* strains, leading to antibiotic treatment failure, increased morbidity and mortality, use of second line antibiotics and increased economic burden. A *Shigella* vaccine could therefore potentially avert a proportion of the AMR burden. As such, the broader population-based benefits, including economic and macro-economic outcomes, will be imperative to describe as part of comprehensive vaccine value assessment.

2. Objectives of the meeting

The objectives for the virtual PDVAC meeting on 18 May 2020 were to:

- seek feedback on the proposed questions, to be addressed by the *Shigella* FVVA.
- identify gaps or other questions that could be addressed as part of the *Shigella* FVVA.

N.B. The purpose of the session was not to use PDVAC as a stage-gate for funding the development of a *Shigella* value proposition.

3. Meeting summary

3.1 Why is WHO's PDVAC advocating for Full Vaccine of Vaccines Assessments (FVVA)? (Birgitte Giersing, WHO)

The FVVA for vaccines is a concept that describes the global value of a vaccine, including from a LMIC perspective. It aims to articulate the full direct and indirect effects of a vaccine. The intent of FVVA is to align stakeholders with respect to the data, gaps and assumptions, and to support

decision-making across the continuum of vaccine development and uptake with a line-of-sight to sustainable socio-economic and public health impact. WHO is engaged in developing FVVAs for a number of vaccines in development, including Group A strep, Group B strep, herpes simplex virus and novel delivery technologies.

A FVVA is an evolving compilation of critical data and evidence-based analysis to rationalise the investment in and prioritisation of vaccines for development, and ultimately for policy recommendation, procurement, and introduction in countries. FVVAs consider the vaccine's strengths and weaknesses in the broader context of interventions that compete for resources, including vaccines for other diseases and other interventions that may have a comparable public health impact. The aspiration for WHO's FVVA approach is to develop a structured framework that provides guidance on the types of data and evidence that will inform decision making, across the product development to vaccine uptake and impact continuum, and to enable – to the extent possible – harmonisation and comparison of FVVAs for different vaccines. In addition, the aims of the WHO FVVA approach are to:

- inform and align different stakeholders over the course of the vaccine life cycle, serving as an end-to-end compendium
- articulate the 'full' potential impact that a vaccine may have, i.e. beyond the traditional metric of lives saved, such as, to quantitate impacts of morbidity, quality of life, and population benefits; to identify the truly critical information, and information gaps; and, to advocate for those information gaps to be addressed
- ensure preferences of intended beneficiaries are clearly articulated and that resources and effort align with these needs, so that there is not a 'valley of death' between vaccine licensure, policy and uptake.
- act as a guiding tool for stakeholders in countries' ministries of health and public health officials to prioritize the country's healthcare expenditure

The FVVA is not a marketing or advocacy tool and will expand over the course of vaccine development as new data come to light and the competitive environment evolves. Ultimately, it aims to proactively prepare for and facilitate policy recommendations and successful vaccine adoption & introduction. The FVVA also informs the WHO preferred product characteristics (PPC) for a class of vaccines.

A draft WHO preferred product characteristics (PPC) document is under development for *Shigella* vaccines. It is crucial that the guidance related to preferences for vaccines aligns with the value assessment, and vice versa.

3.2 Why do we need a FVVA for Shigella vaccines? (Bill Hausdorff, PATH)

Shigella vaccine candidates are at a critical juncture: based on a number of different platforms, the most advanced *Shigella* vaccine candidates have demonstrated proof-of-concept in controlled human infection models (CHIM) and are in phase I/II clinical studies as quadrivalent formats. They are approaching significant investment decisions as they advance towards phase III studies, including the need for pilot-scale manufacturing. In some cases, this will require partnership and technology transfer to vaccine manufacturers.

Funders, partners and other stakeholders need a compelling justification to inform their investment decisions. In particular, clarity is needed to define if - and under which assumptions - *Shigella* vaccines will be taken up into immunization programmes in LMICs.

The PATH *Shigella* FVVA aims to listen to and query stakeholders, including those at the national, regional and global level on the following:

- **Disease target**: What exactly are *Shigella* vaccines seeking to prevent, and why? How effective do the vaccines have to be, also considering the benefit to the overall population?
- **Target population and feasibility of delivery**: who are the vaccines for and is it feasible to deliver them to that target group?
- **Competitive context**: would these vaccines be a preferred, cost-effective solution compared to other pediatric and/or public health interventions?
- **Demand**: what are the perspectives of national and local stakeholders? how is potential impact and cost-effectiveness measured? Does this translate into credible demand forecasts?

Specifically, PATH is positioning their FVVA around three key elements:

1. The evolving perception of *disease burden*: given that mortality of *Shigella* is decreasing, how important is the impact of stunting and its associated long-term sequelae, and how robust is this association? What about antibiotic resistance, potential for outbreaks and the need to control disease in older age groups?
2. New/additional approaches to determine *cost-effectiveness*: What metrics and methods are needed to evaluate the broader impact of stunting and other sequalae? How heterogenous is the disease burden and what is are the ramifications on implementation strategy, or considering combinations in the long-term? How important—and robust—is macro-economic assessment of the impact of stunting in rationalizing the need for a *Shigella* vaccine?
3. National policy maker/end user *perceptions*: How much is known about the awareness and demand, especially in light of an increasingly crowded EPI schedule? How would these vaccine be delivered? What data would drive prioritization and decision-making? How do we ensure we (try to) collect that data prior to licensure?

Discussion:

It is important to define 'value' from the perspective of different stakeholders along the product development to impact continuum - for *Shigella* vaccines in their current stage of development, an investment case will be needed for manufacturers to drive the vaccine through late-stage development. There are data gaps that will either have to be addressed through qualified assumptions, or through data generation.

Understanding the end goal is crucial. It will be challenging to engage with country partners to introduce another vaccine for a diarrhoeal disease without defining the full value of vaccines, and how vaccines for a specific pathogen would impact the broader diarrhoeal picture. Country contexts are very different, and this will influence the preferred delivery route, and strategy.

Understanding the trade-offs from country stakeholders' perspectives will help to identify what data are critical for decision making. This informs the target product profile/WHO PPC, and product development strategy.

- PATH's objective in developing a *Shigella* FVVA is to evaluate the business case for vaccine funders and developers, on the basis of improved/more robust information from in country stakeholders. The FVVA is intended to critically evaluate the available evidence and align around it to determine if there is a favourable value proposition.

3.3 What has changed in our perception of Shigella burden in the last decade (Karen Kotloff, University of Maryland)

In addition to the questions outlined above, there are several unknowns with respect to how we define *Shigella* mortality, morbidity and broader burden:

- What disease manifestations are we seeking to prevent - all Shigella-associated acute watery diarrhea and dysentery, or moderate-to-severe disease (MSD) and how should this be defined?
- How clinically significant is the impact of asymptomatic disease – and if we aim to prevent it, we need a vaccine that induces sterile immunity to interrupt transmission
- What is known about the secondary and indirect effects: how much malnutrition and stunting could a vaccine prevent? What is the impact of, and on, the microbiome in these contexts? What is the role of Environmental Enteric Dysfunction (EED) in malnutrition and stunting? Shigella is found worldwide, but impoverished communities may experience more severe disease.
- With respect to AMR, will a vaccine reduce the use of antibiotics for diarrhea and dysentery? If we don't have a vaccine, will the prevalence of highly AMR strains increase, eventually rendering Shigella untreatable?

With respect to mortality, Shigella is currently considered the 2nd leading cause of diarrhea-mortality (13.2% of diarrheal deaths (95% CI 9.2-17.4)), causing >50,000 deaths in children under 5 each year according to IHME, with an additional burden due to the effect of growth faltering. These estimates are informed by several studies including GEMS, GEMS 1A and VIDA, which are case-controlled, population-based studies to measure the incidence, etiology, and adverse clinical outcomes of diarrheal illness among children <5 years of age living in LMICs. GEMS and GEMS 1A assessed mortality before introduction of rotavirus vaccine (RV), and VIDA assessed the impact following RV uptake. In GEMS, the cases were defined as those that sought healthcare with new onset acute diarrhea, with at least one of sunken eyes, loss of skin turgor, IV rehydration, history of bloody diarrhea and/or hospitalization (actual or recommended). GEMS 1A included patients with lower severity diarrhoea (LSD), where eligible cases sought healthcare with new onset, acute diarrhea without any of the MSD signs.

Other data from Child Health and Mortality Prevention Surveillance (CHAMPS) study may provide further data, however it may be a challenge to definitively link PCR positivity with death. The CHAIN (Childhood Acute Illness and Nutrition) study in Bangladesh, Burkina Faso, Kenya,

Malawi, Pakistan, Uganda will also bring more insight, aiming to recruit ~3000 hospitalized children with oversampling of malnourished children (~1700 children admitted with diarrhea) and measurement of LAZ, WHZ among other end points. To date 19% of patients have tested positive for *Shigella*.

With respect to *Shigella*-specific morbidity, IHME published diarrhoeal global incidence for <5 years as 11.6/100 c-y (95% CI 6.4-19.9). GEMS, GEMS 1A, and VIDA also assessed *Shigella*-specific morbidity. Comparing attributable incidence between GEMS and VIDA, only rotavirus significantly declined following RV introduction in 0-11 months; by the 12-23-month age *Shigella* has the greatest attributable incidence and remains highest at 24-59 mo. If the incidence of LSD is included with MSD, the incidence doubles.

Data from MALED, a community-based cohort study, is incorporated into IHME mortality estimates for *Shigella* and morbidity estimates for diarrhea. This study expanded the geographical coverage to include Latin America and the attributable incidence markedly increased when community cases are included. In MALED, MSD incidence rates were consistent with those seen in GEMS, so there is a consistent aetiologic pattern across GEMS, GEMS 1A, VIDA and MALED as well as prior epidemiologic studies.

The ABDC (Antibiotics for Children with Diarrhoea) Trial Network is undertaking a double-blind placebo-controlled trial of azithromycin to reduce mortality and increase growth in high-risk 2-24mo old children with non-bloody diarrhoea in low resource settings. The trial is underway, and will expand the geographical coverage of *Shigella* aetiology generating data from Mali, Malawi, Pakistan and Bangladesh. It also assesses a different population of 2-23-month children who have no dysentery, and who are not using antibiotics, with primary outcomes of mortality and length-for-age z-score (LAZ). Preliminary data suggest that the prevalence of *Shigella* ranges between 10-30% across the 6 sites in AFRO and SEARO, based on quantitative PCR, and that a positive impact on growth results when children with *Shigella* infection are treated with azithromycin.

Longer term outcomes of shigellosis have been assessed in GEMS, GEMS 1A, and VIDA, which were conducted sequentially over a 10-year period. These studies measured the impact of overall MSD and LSD, and Shigella-specific MSD over 90 day follow up. The findings have been similar in each study. VIDA, the most recent study, demonstrated that height for age (HAZ)-scores at enrollment for MSD cases & controls by age stratum (0-11mo, 12-23mo, 24-59mo) on day 0 were not significantly different, but after an episode of MSD, the decline in HAZ was more pronounced, especially for infants. The gradient was significantly greater in cases vs controls over the follow up period for all 3 age groups ($p \leq 0.003$). Similar findings were observed in the less severe diarrhea cases studied in GEMS 1A, illustrating a more widespread impact of diarrhea on linear growth. . This observation of linear growth shortfalls, even in the absence of diarrhoea was confirmed by investigation of diarrhoeal and non-diarrhoeal stools collected from children in the first 2 years of life obtained during MALED; sub-clinical infection with Shigella has a negative associated with linear growth.

Finally, protection against serogroups and serotypes not contained in a vaccine (heterotypic immunity) will be important to assess; if cross-protection among *S flexneri* serotypes is observed,

then a vaccine containing *S sonnei* and *S flexneri* 1b, 2a, 3a, and 6 O-antigens could provide coverage for up to 90% of *Shigella* strains.

Discussion:

PDVAC agrees that there is a clear need to develop a FVVA to articulate the broad impact a vaccine could have, and to assess the relative need and demand for *Shigella* vaccines in the context of other interventions.

There are data gaps related to the long-term impact of *Shigella* infection, the impact on the microbiome, and in particular the effect of asymptomatic or sub-clinical infection on stunting. Liz Rogawski's data from MALED suggested asymptomatic shigellosis had most profound impact on linear growth faltering, more so than other diarrhoeal pathogens and symptomatic illness. In contrast, in GEMS, children symptomatic with MSD have significant growth faltering. Given that the ability to produce sterilizing immunity against Shigella is may not be feasible, we need to better characterise the impact of less severe/asymptomatic disease.

An additional consideration for the FVVA for *Shigella* is related to the potential decline in measles coverage as a consequence of Covid-19, since the severity of shigellosis is understood to be worse in children who have had measles. The burden of *Shigella* could increase in the post-Covid context.

The nutritional aspect is crucial; malnutrition results in a vicious cycle of repeated infections and malnutrition, that is hypothesised to be mediated by the phenomenon of Environmental Enteric Dysfunction (EED). It can also lead to changes in microbiome that affects immunological function and ability to respond to *Shigella* (and prevent stunting) or other infections and could also compromise the vaccine response.

3.4 AMR as an incentive for Shigella vaccine development and use (Mateusz Hasso-Agopsowicz, WHO)

Global estimates suggest that drug-resistant infections currently result in 700,000 deaths per year and could rise to 10 million annual deaths by 2050, with economical expenditure of US$10 trillion. The WHO, UN, international organizations, member states and public health stakeholders are collaborating to produce a list of recommendations to combat AMR, and vaccines have been highlighted as having an important role in the process, by a) preventing the infection and reduce carriage and transmission of AMR pathogen, and b) reducing the presence of clinical symptoms, reducing the pathogen associated antibiotic use. This is exemplified by typhoid, which is anticipated to cause 3,695,000 cases over the next 10 years if no vaccine is implemented, 2,6000,000 of which are expected to be extensively drug resistant. A vaccine, such as the recently WHO recommended Typhoid conjugate vaccines, would avert an estimated 1,272,000 typhoid cases over 10 years after introduction, of which 70% would be extensive drug-resistant cases. This analysis catalysed the decision to introduce TCV into Pakistan and provided the impetus to attempt to quantify the broader public health and economic value that a vaccine could bring in the control of antibiotic resistant pathogens. A thorough and systematic understanding of a value of

vaccines such as typhoid and other on the impact on AMR is needed to support decision making around vaccine development, introduction and use.

As such, the WHO is developing an action framework to concretely strengthen the role of vaccines in the fight against AMR, as well as a value attribution framework to articulate the value of vaccines against AMR. The value attribution framework aims to define this value according to a list of criteria, including vaccine-averted AMR health burden, vaccine-averted economic burden, vaccine-averted antibiotic use. The impact of *Shigella* vaccines will be evaluated as part of this framework, assuming the product attributes that are under development within the WHO preferred product characteristics guidance. The preliminary estimates are expected to be available in late 2020 to inform the *Shigella* FVVA.

The ability of *Shigella* vaccines to impact the AMR health and economic burden as well as antibiotic use associated with other enterobacteriae will not be included in the analysis, however, AMR impact may be investigated in trials where *E.coli* is more common.

3.5 The potential impact and cost-effectiveness of a Shigella vaccine (Farzana Muhib, PATH)

The current evidence available to estimate the burden of *Shigella* was briefly reviewed. In addition to direct deaths from *Shigella* infections, Anderson et al estimated that an additional 2.1 million children would suffer from growth stunting and increased susceptibility to other infectious diseases, resulting in an incremental 13.2K deaths.

Variable	Annual burden	Sources/assumptions
Direct deaths from Shigella infections	49.4K deaths (36.4K-64.5K)	Used the mid-point estimates (IHME, MCEE 2015)
Shigella cases	111.2M cases (78.8M-149.4M)	Etiologic fraction of all diarrhea (GEMS, Adjusted for PCR)
Moderate to severe stunting cases due to Shigella	2,144K cases (728-3299K)	MSD associated with a shift in HAZ score of 0.082
Additional deaths from other infectious disease	13.2K deaths (4.6K-20.7K)	Population attributable risk for other infectious disease in stunted children (Black et al)

These burden estimates were used to calculate the cost-effectiveness of *Shigella* vaccines, based on the following inputs and assumptions: the mortality and morbidity of a *Shigella* infection in 79 LMICs, a 60% efficacious vaccine against severe *Shigella* disease, 3 doses, DTP3 coverage, and a proxy price of $3.30 per dose (based on the initial price for rotavirus vaccines). Two scenarios were evaluated: one included the incremental deaths as a consequence of stunting, one the other scenario did not. The Incremental Cost Effectiveness Ratio (ICER) was estimated to be approximately $3,000 when the impact of stunting was excluded and approx. $2,500 when it was included.

Vaccine	Results	Sources/assumptions
Shigella excluding deaths due to other infectious diseases and stunting	$3,114 ($2,117-$6,276)/DALY averted (2016$/DALY)	79 LLMIC*, vaccine efficacy of 60%, 3 doses and DTP3 coverage, $3.30 per dose
Shigella including deaths due to other infectious diseases and stunting	$2,513 ($1,708-$5,088)/DALY averted (2016$/DALY)	79 LLMIC*, vaccine efficacy of 60%, 3 doses and DTP3 coverage, $3.30 per dose
Rotavirus	$325/DALY averted (2015$/DALY)	73 "Gavi" countries, vaccine efficacy of 44-77% at 12 months, 2 or 3 doses, $0.85-$3.2 per dose
Malaria	$87 ($48-$244) averted (2013$/DALY)	*Pf*PR_{2-10} (3-60%), vaccine efficacy 43·9% (95% CI 39·7–47·8) over 32 months, 4 doses, $5 dollars per dose

Implications: *Shigella* mortality is lower than some other vaccine preventable diseases, and vaccine cost-effectiveness is driven by number of deaths averted. Therefore, when using a standard ICER comparison metric, *Shigella* vaccines are less likely to be attractive compared to other vaccines that are available. However, the burden of *Shigella* goes beyond mortality, and the broader impacts of morbidity need to be captured and quantified, including the long-term sequelae and the associated potential linkages to reduced cognition, chronic conditions (such as cardiovascular disease), and increased susceptibility to other infectious diseases. Beyond the individual effects, the broader implications of disease, including impact on schooling, utilization of health services, future economic prospects, and macroeconomic impact need to be assessed and included in the value assessment. These effects are inter-related, so the broader considerations for determining *Shigella* vaccine impact and cost-effectiveness include the ability of *Shigella* vaccines to reduce impoverishment, increase productivity, and improve equity. Reduced risk of loss of household income due to death or long-term effects increases the probability of improved nutrition from a young age, which in turn reduces susceptibility to other infectious diseases.

Novel approaches and methodologies are needed to frame the economic case for *Shigella* vaccines that quantify the impact of infection on stunting, cognition, broader susceptibility, and educational attainment, as well as the macroeconomic effects. In addition, there are significant epidemiological and economic information gaps that hamper the elucidation of the full value of *Shigella* vaccines. With this in mind, PATH proposes the need to build and populate a macroeconomic framework that can use available data to understand both magnitude and uncertainty associated with different factors, and to use this to guide prioritization of research to fill these gaps.

Questions for discussion with PDVAC:

Q1: Burden:

- Assumes *Shigella* mortality burden alone will not be sufficient to drive development of, and policy recommendation for, *Shigella* vaccines.
- In addition to revised assessments of the *Shigella* short term morbidity burden, suggestive data link *Shigella* infections to stunting, and prevention of stunting to economic and macroeconomic outcomes.

  - Do you consider a comprehensive analysis of the robustness and magnitude of these associations, based on current data, to be a critical part of a FVVA of *Shigella*?

  - Do you consider a macroeconomic assessment of *Shigella* vaccines' impact on stunting, other long-term sequelae to be a timely and critical part of the FVVA?

  Yes, the Shigella FVVA should include a full assessment of data and analysis related to the impact of stunting as a consequence of Shigella infection, and its long term effects – however, since growth faltering is related to a variety environmental and pathological factors, the focus should not be solely on the ability of a Shigella vaccine to prevent stunting (as opposed to infection or disease).

  Need to look for opportunities to examine the effect of stunting in clinical studies; probe studies may inform as to the optimal metrics and limitations of cost-effectiveness and vaccine impact models, and practically, how data may be collected.

  Undertaking a macro-economic analysis of Shigella impact will be challenging, since there are many confounders, and little precedence for this from other vaccines, but these kind of data will be needed to inform decision makers at the country level with respect to Shigella, and other vaccines/interventions. We need to move the field in this direction, and the methods developed for Shigella will help to pave the way for other diarrhoeal diseases.

Q2: Vaccine impact and cost effectiveness modelling:

- Assumes inclusion of direct and indirect effects due to stunting, AMR, and consideration of a combination vaccine, would provide more favourable cost-effectiveness assessment

  - What modifications, if any, to current cost-effectiveness analyses should be included based on new data, or understanding of the disease, AMR impact or epidemiology?

  The impact on healthcare utilization needs to be included in the FVVA.

  For AMR, Shigella vaccines' ability to reduce the use of antibiotics and AMR emergence in other in enterobacteriae, e.g. E.coli, would be important to quantify, and this is not planned to be included in the analysis that is currently planned under the AMR value attribution framework.

  - (When) should we model the incremental cost-effectiveness ratio for different vaccine combinations?

The FVVA for stand-alone Shigella vaccines needs to be undertaken initially, to determine if a stand-alone has a compelling value proposition but also to be able to evaluate how the value proposition would change incrementally in the context of a combination vaccine. It is anticipated that the cost-effectiveness of a Shigella vaccine would increase when included as part of a combination vaccine. Determining which combination vaccines would have favorable value propositions is anticipated to incentivize development of Shigella-containing vaccine.

Q3: Understand end-user preferences and demand:

- Assumes systematically assessing LMIC interest and priorities, as candidates progress along the product development continuum, is crucial to 'pull' Shigella vaccine development and help shape the vaccine attributes.
- Assumes this is a key part of a FVVA to de-risk and incentivize investment for manufacturers.
    - How, and when, should we engage with / gather information on current national stakeholder and health care practitioner perceptions of Shigella burden and of a vaccine's potential impact on diarrheal disease burden?

The FVVA is not a static document; it is a compilation of existing evidence but also a dynamic process of stakeholder engagement and alignment around the data, gaps and strategic directions. Consolidation of this stakeholder engagement and communication needs to occur throughout vaccine development and subsequently lead to further refinement of the FVVA.

The health-economic lens may be different to the public health decision-making priorities and criteria – global stakeholders and vaccine developers need to understand the priority criteria of countries to inform the FVVA and evidence generation approach. PDVAC strongly advocates for the use of the FVVA approach to build awareness and early global stakeholder alignment.

The decision-making contexts and drivers within LMICs differ and are dynamic. MALED and GEMS are already 10 years old; will the data from these two studies still be relevant in decision-making a decade from now when Shigella-containing vaccines may be ready for introduction? Country and regional engagement are key to understanding current priorities and how these priorities have changed over time.

Start times:

06:00 Seattle; 8:00 Lima; 9:00 Washington DC; 14:00 London; 15:00 Johannesburg; 15:00 Geneva; 18:30 New Delhi, 21:00 Beijing; 22:00 Seoul

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
15.00 – 15.10	Introduction: session overview & objectives			David Kaslow / Birgitte Giersing
15.10 – 15.20	Why do we need a FVVA for Shigella vaccines?	10’	**For information:** Overview of proposed key elements that are needed to define the Shigella vaccine value assessment	Bill Hausdorff (PATH)
15.20 – 15.30	Questions for clarification			
15.30 – 15.55	What has changed in our perception of Shigella burden in the last decade?	15 + 10	**For information:** Evolving mortality estimates, subnational vs national heterogeneity, recent data or models that many inform impact of stunting	Karen Kotloff (UMD)
15.55 – 16.10	AMR as an incentive for vaccine development/use	10 + 5	**For information:** Overview of ongoing studies of potential impact of a Shigella vaccine on AMR	Mateusz Hasso-Agopsowicz (WHO)
16.10 – 16.25	The potential impact and cost-effectiveness of a Shigella vaccine.	10’ + 5’	**For information:** Includes an overview of key impacts considered and omitted and the rationale for considering the relationship between stunting, cognition, learning and macroeconomic effects.	Farzana Muhib (PATH)
16.25 – 16.30	Questions for consideration	5’	**For discussion and input:** ➢ Do you consider a comprehensive analysis of the association of Shigella with stunting and AMR to be a critical part of a FVVA of Shigella? ➢ Do you consider a macroeconomic assessment of a Shigella vaccine’s impact on stunting and other long-term sequelae to be crucial? ➢ What modifications, if any, to current cost effectiveness analyses should be included based on new data, or understanding of the disease, AMR impact or epidemiology?	Birgitte Giersing (WHO)

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
			➢ (When) should we model the incremental cost-effectiveness ratio for different vaccine combinations? ➢ How should we engage with / gather information on current national stakeholder and health care practitioner perceptions of Shigella burden and of a vaccine's potential impact on diarrheal disease burden, stunting, and AMR, either as a standalone or a combination, to help determine vaccine preferences, affordability and access requirements and to inform vaccine demand analyses?	
16.30 – 17.00	Discussion (open session)			
17.00 . 17.30	Discussion (closed session)			