2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 2: Update from the Burden of Enteric Diseases working group
11 May 2020

Participants:

WHO: Martin Friede, Birgitte Giersing*, Geraldine Griffin, Mateusz Hasso-Agopsowicz*, Erin Sparrow

Chair of SAGE: Alejandro Cravioto

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

Observers and non-member participants: Julia Baker*, Louis Bourgeois, Robert Breiman*, Matt Doxey, Robert Black, William Hausdorff, Ibrahim Khalil, Jens Kieckbusch, Hmwe Kyu, Benjamin Lopman*, Cal MacLennan, Sophie Mathewson, Deepali Patel, Virginia Pitzer*, James Platts-Mills*, Duncan Steele

*denotes BoED working group members

Executive Summary

Rationale for topic: In 2018, PDVAC recommended that an expert working group be established to explore the differences between IHME and MCEE under 5 mortality estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based.

General conclusions:

- Results from systematic reviews of odds ratios (ORs) of developing diarrhoea when a pathogen is detected in stool, and pathogen-specific case fatality rates (CFRs) were presented. Results are stratified by a pathogen, child mortality strata, detection method, and study setting. There is heterogeneity between pathogens for both CFRs and ORs. Suggestions were made how results of these analyses could inform future iterations of mortality estimates;
- Results from the study quality grading analysis were presented. The majority of studies for ETEC and Shigella are considered of good quality (>70% of quality score). A sensitivity analysis will be conducted to measure the impact of low-quality studies on mortality estimates;
- The IHME diagnostic test adjustments increase the Shigella mortality estimate by approximately twofold but do not increase the ST-ETEC estimate; the other IHME adjustments have a negligible impact on the estimates;

- IHME and MCEE expressed enthusiasm about the presented work and presented ideas on how these results could improve future mortality estimates;
- PDVAC felt that the outcomes of the BoED WG will lead to improved understanding of data processing and data inputs that inform the mortality estimates, and could improve their robustness and credibility;

PDVAC Recommendations:

- *A set of publications with proposed recommendations for inclusion and exclusion criteria for studies will be an important contribution.*
- *Results of all analyses should be represented visually on a map to highlight countries with no data or countries where data quality is low;*
- *Additional PCR, hospital-based, multi-pathogen studies, such as from GPDS, should inform future mortality estimates.*
- *By the time a vaccine for ETEC or Shigella is developed and licenced, mortality might be one of the drivers in the full value of vaccine assessment (FVVA), and it should be considered together with other components such as morbidity, educational attainment, antimicrobial resistance, economic burden and healthcare utilisation;*
- *PDVAC agrees with the proposed scope of morbidity work; however, the committee highlighted that the scope should be focussed to inform strategic decisions around vaccine development investment, policy recommendation, and vaccine introduction and use.*
- *PDVAC recommended to engage early in the process with multiple stakeholders (NITAGs, RITAGs, SAGE, vaccine developers, GAVI) to ensure that results from the proposed morbidity workstreams will drive decision making*
- *Identify elements in the FVVA that are specific to particular enteric pathogens and the ones that are applicable to a broader group of pathogens.*

1. Context and format of the meeting

Investment in vaccine product development and policy decisions for introduction are informed by the impact that the vaccine is expected to have on disease burden, which currently is mainly driven by the mortality burden. However, there is often a lack of epidemiological data to inform vaccine impact assessments and cost-effectiveness studies, and decisions are based on burden models that extrapolate from specific studies in which disease data are collected. Policy decisions are mostly informed by the extent to which a vaccine might reduce mortality and do not adequately consider the effect the vaccine may have on the morbidity burden, or broader population-based implications.

A number of enteric vaccine candidates are in clinical product development, including those to address the burdens of *Shigella*, enterotoxigenic *E.coli*, norovirus and non-typhoidal *Salmonella*. As part of its mission to advance vaccine development that addresses significant unmet public health need globally, WHO is embarking on efforts to better evaluate and communicate the full value of vaccines, while candidates are in the early stages of product development. The Full Vaccine of Vaccines Assessment (FVVA) is a concept that describes the full value of a vaccine and aims to articulate all direct and indirect effects. The intent of 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.

Two main modelling groups provide mortality estimates for enteric pathogens: the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle, and the Maternal Child Epidemiology Estimation (MCEE) group, led by Johns Hopkins Bloomberg School of Public Health. In 2018, PDVAC reviewed the global diarrhoea mortality estimates for under five-year-olds from these two groups. While estimates from the two groups a decade ago were closely aligned, more recent estimates for 2016 have diverged, particularly with respect to numbers of deaths attributable to different enteric pathogens. This has impacted prioritisation and investment decisions for candidate vaccines in the development pipeline. For this reason, PDVAC recommended the formation of an independent working group of subject matter experts to explore the reasons for differences between the IHME and MCEE estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based.

While infections with enteric pathogens result in substantial mortality, the morbidity impact due to malnutrition, stunting, and cognitive impairment can last long after the initial infection took place. To comprehensively assess the full vaccine value and inform vaccine prioritisation and use, both mortality and morbidity need to be explicitly quantified. However, there is a lack of consensus on how to measure, analyse and present morbidity associated with enteric infections, and as such, the value of enteric vaccines is under-estimated.

This PDVAC session reviewed the outputs of the BoED WG group since the 2018 PDVAC recommendation and discussed the potential expansion of the scope of this group to evaluate current data and methodology to assess morbidity for these pathogens.

Objectives of the meeting

The objectives for the virtual PDVAC meeting on 11 May 2020 were to:

1. Review the status of workstreams related to improving quantification of the under-five mortality caused by individual enteric pathogens;
2. Discuss the impact of findings and their potential implications for the future under-five mortality estimates;
3. Provide an overview of the proposed expansion of the working group scope to evaluate the data and methodology to quantify the morbidity burden of enteric pathogens.

2. Summary of workstreams and the BoED process to date

The BoED WG was convened in November 2018 to assess the differences in the methods used to derive the U5 mortality estimates, increase the understanding of data incorporated into the models, and increase the transparency and credibility of the estimates. The WG proposed to engage in four workstreams, and all were later reviewed and endorsed by both PDVAC and IVIR-AC:

1. Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates.
2. Study Quality Exercise – to improve the understanding and quality of the studies included in the modelling process.
3. Data Processing Exercise – a high-level assessment of similarities and differences in study data included in the models and how it is processed.
4. Model Comparison Exercise – to address structural and methodological differences in models: on hold, pending results from workstreams 1-3.

3. Workstream 1: Data Gaps

Rationale: the purpose of this workstream is to identify and address areas of commonality between the IHME and MCEE methods, where additional evidence may improve future estimates. The BoED WG recommended to conduct two systematic reviews:

1) Systematic review and meta-analysis of odds ratios of developing diarrhoea when a pathogen is detected in stool;
2) Systematic review and meta-analysis of pathogen-specific case fatality rates.

3.1. Results from the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool.

Rationale: The IHME estimates for the number of episodes and deaths attributable to each pathogen are the product of the total number of diarrhoea episodes and deaths, and the population attributable fraction (PAF) for that aetiology. To calculate PAF, odds ratios (ORs) of developing diarrhoea when a pathogen is detected in stool are used. IHME uses ORs from

seven sites of The Global Enteric Multicenter Study (GEMS) and extrapolates them globally. Consequently, the BoED WG proposed to conduct a systematic review to better understand the heterogeneity of pathogen-specific ORs across under 5 (U5) mortality strata, age groups, and pathogen detection methods.

Methodology: The START Centre at the University of Washington conducted a systematic review of the literature (1990-2019) and identified 145 suitable studies, including 1324 observations for 15 pathogens. GEMS and Malnutrition and Enteric Disease Study (MAL-ED) studies were included. Julia Baker and Benjamin Lopman (Emory University) developed a model to calculate ORs stratified by pathogen, age group, detection method, and child mortality strata.

Results: There is substantial heterogeneity of ORs by pathogen, age, child mortality strata and pathogen detection method. ORs reflect the frequency of exposure, asymptomatic infection, development of immunity, and they may be adapted and used as inputs in burden models. Table 1 summarises results of the OR analysis.

Table 1. Summary of results for the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool (unpublished, confidential).

Pathogen	Unadjusted*		0-5 years**						> 5 years*	
			V. low mortality		Low morality		High mortality			
	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI
Adenovirus	2.1	1.8-2.6	6.4	1.0-38.8	4.1	1.9-8.8	1.3	0.8-2.1		
Astrovirus	1.9	1.6-2.3			0.6	0.1-3.0	1.7	0.9-3.1		
Norovirus	1.7	1.4-2.0			9.8	1.7-57.3	2.9	1.4-6.0	3.2	1.3-7.6
Norovirus GI	1.4	0.7-3.0			1.6	0.5-5.2	0.8	0.5-1.2	1.4	0.4-4.4
Norovirus GII	2.1	1.6-2.9			4.6	2.6-7.9	0.9	0.3-2.8	3.4	1.3-8.8
Rotavirus	6.4	5.6-7.3	7.9	1.9-32.9	7.2	3.5-15.2	5.9	4.1-8.4	2.9	1.3-6.5
Sapovirus	1.8	1.5-2.1			2.0	1.4-2.8	1.0	0.5-1.8		
Aeromonas	2.4	1.7-3.3					3.7	3.2-4.2		
Campylobacter	1.7	1.5-1.9	8.8	1.3-59.2	2.3	1.2-4.4	1.7	1.3-2.2	5.1	2.6-10.0
Cholera	5.3	1.6-17.1								
EPEC	1.4	1.2-1.6	1.8	1.2-2.7	2.8	0.6-13	1.4	0.9-2.0	1.2	0.9-1.7
ETEC	1.8	1.6-1.9	2.0	0.8-5.1	0.5	0.3-0.9	1.5	1.2-1.9	1.4	0.1-24.7
ST ETEC	2.2	1.9-2.6	2.4	0.7-8.1	0.9	0.5-1.5	1.6	1.1-2.5	4.8	1.7-14.2
LT ETEC	1.1	1.0-1.3	0.6	0.3-1.4	0.4	0.2-1.0	1.0	0.7-1.4	1.2	0.2-6.3
Salmonella enterica	1.9	1.4-2.5			1.4	0.9-2.0	1.4	0.8-2.5	0.9	0.6-1.3
Shigella	5.5	4.3-7.1			4.6	2.1-9.8	4.2	2.4-7.3	2.8	1.5-5.5
Cryptosporidium	2.2	1.9-2.4	2.5	1.2-5.2	1.0	0.3-3.2	1.9	1.7-2.2	3.4	1.2-9.6
E. histolytica	1.3	1.1-1.6			0.6	0.2-1.9	1.7	1.1-2.7	1.2	0.6-2.3
Giardia lamblia	1.0	0.9-1.1	1.1	0.4-3.0	2.0	0.9-4.4	0.8	0.6-1.1	1.2	0.6-2.3

**All age groups, all mortality strata*

***Controlling for pathogen detection method, study design*

Next steps: The analysis is finished and will be published together with other manuscripts as a series of publications related to this work. WHO together with Benjamin Lopman and Julia Baker will work closely with IHME and MCEE to understand how the results of this analysis may be incorporated into future modelling estimates.

Discussion:

- Due to the heterogeneous study design of this meta-analysis, pathogens were treated independently and the impact of multiple pathogen infections on ORs was not investigated;
- The OR that a pathogen was associated with diarrhoea was more strongly determined by prevalence in controls than prevalence in cases. This finding points out the limitation of using ORs as a measure of pathogenicity for enteric pathogens that confer incomplete immunity;
- Higher ORs are reported for ST-ETEC in very low or low mortality setting vs high mortality settings; however, for Shigella, OR was high and consistent in low to high mortality settings and in over 5 year olds;
- Large uncertainty represented by wide confidence intervals should be taken into account when analysing results;
- The results provide a more granular OR stratification across pathogens, ages and mortality strata, and add to the currently used ORs based only on the GEMS study.

3.2. Results from the systematic review of pathogen-specific case fatality rates (CFRs)

Rationale: Global burden of diarrhoea models assume that deaths from enteric pathogens occur in proportion to the distribution of pathogens in hospitalised (MCEE) or severe (IHME) cases. The estimates do not take into account potential differences in the risk of death from different pathogens. Consequently, the BoED WG proposed to conduct a systematic review to better understand the heterogeneity of CFRs among pathogens, WHO regions, age groups and study settings.

Methodology: The START Centre at the University of Washington conducted a systematic review of the literature (1990-2019) and identified 430 studies for 15 pathogens. Published studies from GEMS and MAL-ED were included. Ernest O. Asare & Virginia Pitzer (Yale University) conducted an analysis to examine heterogeneity in the CFR across pathogens, WHO regions, age groups and study settings, and to develop a model to estimate the overall CFR and the CFR for each pathogen, while controlling for predictors of heterogeneity.

Results: There is substantial heterogeneity in the estimated CFRs both within and between pathogens. For some pathogens, the CFR was higher in children under one year old, living in the AFRO region, or in higher mortality strata. For viral pathogens, the CFR was higher in community-based studies, whereas for bacterial pathogens, the CFR was higher in hospital-based studies. Table 2 summarises results of the CFR analysis.

Table 2. Summary of results from the systematic review and meta-analysis of case fatality rates for diarrheal pathogens (unpublished, confidential). Also shown are the odds ratios comparing the CFRs with that for Salmonella.

Pathogen	CFR	95% CI	Odds ratio	95% CI for OR
	Fixed effects model		***Multi-level mixed effects model†***	
Overall	0.0065	(0.0058, 0.0073)		
Salmonella	0.0028	(0.0026, 0.0030)	REF (1.0)	--
Shigella	0.0302	(0.0287, 0.0318)	1.18	0.67, 2.09
Campylobacter	0.0021	(0.0020, 0.0023)	0.44*	0.24, 0.82
Cholera	0.0107	(0.0106, 0.0108)	0.79	0.43, 1.44
ETEC	0.0304	(0.0470, 0.0195)	1.18	0.52, 2.69
EPEC	0.0637	(0.0546, 0.0741)	3.24*	1.68, 6.26
Rotavirus	0.0006	(0.0006, 0.0007)	0.22*	0.14, 0.36
Norovirus	0.0015	(0.0015, 0.0016)	0.72	0.40, 1.29
Sapovirus	0.0266	(0.0215, 0.0330)	1.25	0.34, 4.55
Astrovirus	0.0034	(0.0016, 0.0070)	2.38	0.84, 6.75
Adenovirus	0.0015	(0.0009, 0.0023)	0.80	0.36, 1.79
Giardia	0.0000	(0.0000, 0.0003)	0.46	0.12, 1.76
Cryptosporidium	0.0049	(0.0041, 0.0059)	1.24	0.59, 2.60
Entamoeba	0.0000	(0.0000, 0.0132)	0.60	0.09, 3.94
Aeromonas	0.0048	(0.0013, 0.0173)	1.71	0.48, 6.14
Other	0.0260	(0.0208, 0.0323)	1.26	0.34, 4.69
Covariates included in full multi-level model				
Age group (REF: Under 5 yrs)				
Under 1 yr			1.39	0.92, 2.10
Above 5 yrs			0.77	0.51, 1.14
Other			0.96	0.64, 1.45
Under-5 Mortality Strata (REF: very low)				
Low			1.83*	1.04, 3.21
High			5.50*	3.30, 9.16
Setting (REF: hospital)				
Community			0.80	0.47, 1.34
Other			0.76	0.36, 1.62

†Accounts for between-study (and within-study) heterogeneity using random effects
*Denotes $p<0.05$

Next steps: Virginia and Ernest are finalizing models to calculate pathogen-specific CFRs while controlling for potential predictors of heterogeneity. Once finished, the analysis will be published together with other manuscripts as a series of publications related to this work. WHO together with Virginia Pitzer and Ernest O. Asare will work closely with IHME and MCEE to understand how the results of this analysis may be incorporated into future modelling estimates.

Discussion:

- Calculated CFRs are similar to the ones calculated using the data from the WHO Global Rotavirus surveillance network;

- Observed differences in CFRs between hospital and community studies might reflect the clinical course of a disease. Short-lasting viral infections would most likely present and cause deaths in a community, whereas longer-lasting bacterial infections would likely present and cause deaths in a hospital;
- Data on the proportion of dying children that have access to a hospital could help to adjust for variations in access to treatment and its impact on CFR;
- Studies conducted in communities introduce community interventions that change the underlying epidemiology of diseases and access to treatment in that population. They should be interpreted with caution.
- Hospital-based CFRs account for treatment access and could be used to inform future mortality estimates.

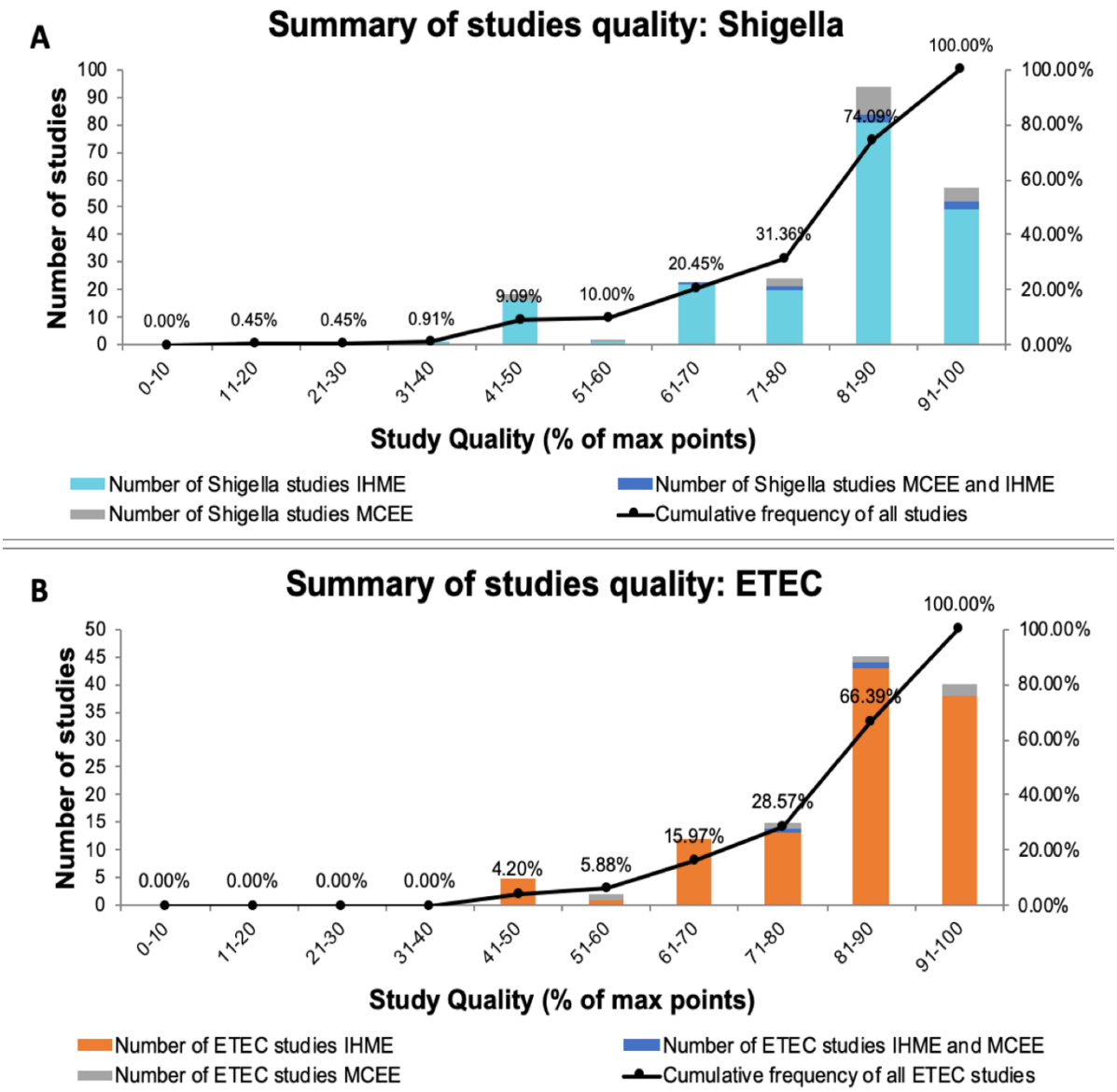
4. Workstream 2: Study Quality Exercise

Rationale: There is a limited understanding of the type and quality of studies that are used to calculate mortality estimates by both IHME and MCEE. The BoED WG suggested conducting a quality grading review of all ETEC and Shigella studies to determine the quality of the studies used by each of the groups.

Methodology: Egle Butkeviciute (LSHTM), together with the BoED WG, developed a modified Newcastle-Ottawa Scale (NOS) to assess the quality of IHME and MCEE studies. To determine the study quality, the NOS considers selection, comparability and outcome criteria. A total of 119 studies were graded for ETEC and 220 for Shigella.

Results: Out of 119 studies for ETEC, only two were used by both IHME and MCEE; and out of 220 studies for Shigella, only eight were used by IHME and MCEE. The limited overlap is a reflection of different inclusion criteria that are adopted by the groups. For Shigella, 20.45% of studies scored less than 70/100 quality score (figure 1A); for ETEC, 15.97% scored less than 70/100 quality score (figure 1B). Similar quality scores were observed for studies used by both groups, both for ETEC and Shigella.

Figure 1. Results of the quality grading analysis for ETEC and Shigella (unpublished, confidential).



Next steps: The grading analysis is finished and WHO is working closely with IHME to conduct a sensitivity analysis of low-quality studies and their impact on mortality estimates. The results of the grading and sensitivity analyses will be incorporated into a publication that articulates high-level recommendations for studies to be included in reports of mortality estimates.

Discussion:

- This analysis was focused on identifying study characteristics that could lead to bias in interpreting results;

- The sensitivity analysis of low-quality studies will focus on the IHME dataset as 1) a small number of studies included in the MCEE model would prevent informative analyses, and 2) MCEE's approach to calculating mortality estimates has evolved since 2013, data gaps were identified, and the estimates were not published.

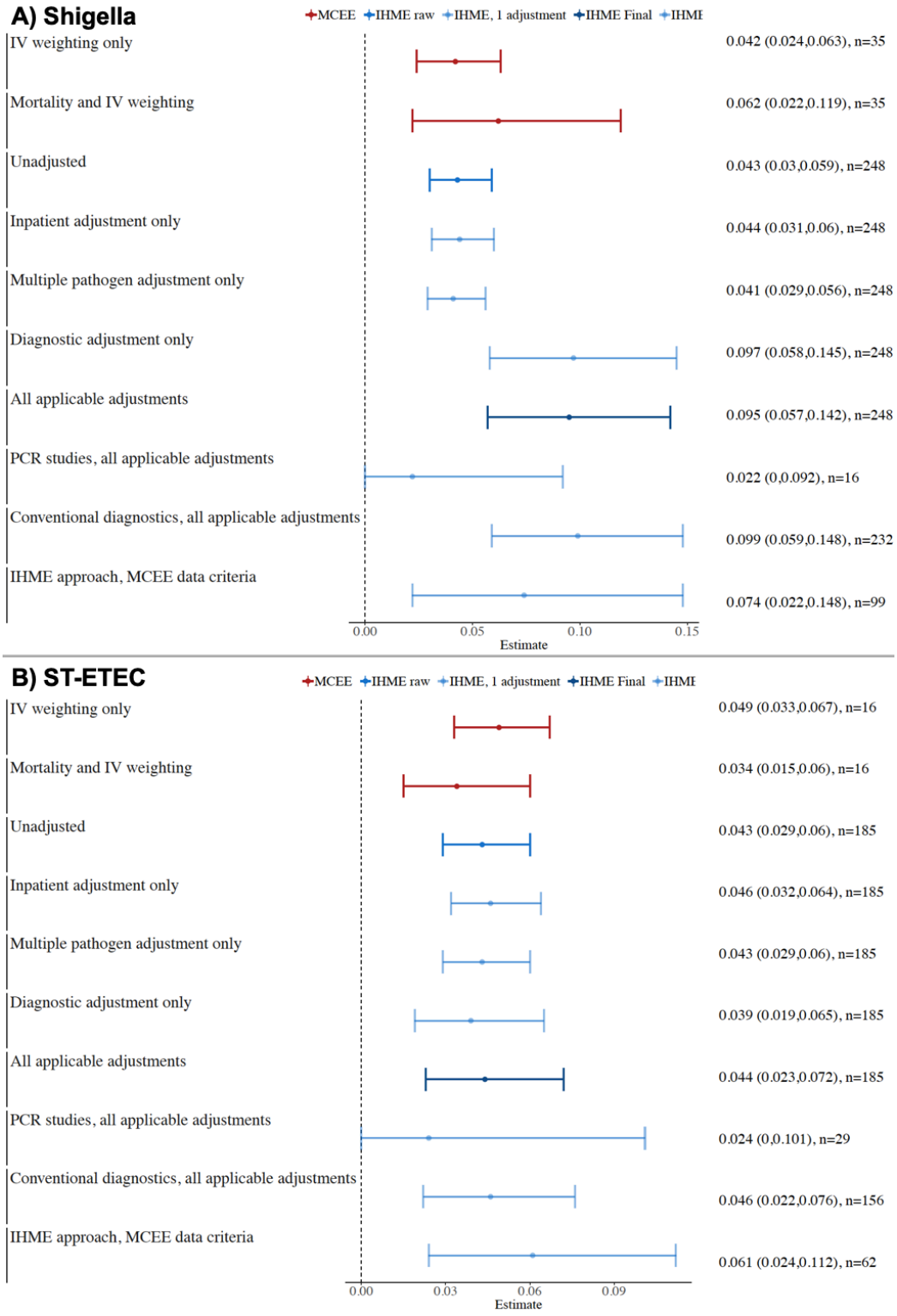
5. Workstream 3: Data Processing Exercise

Rationale: There is a limited understanding of how data used by IHME and MCEE compare, before and after applying model adjustments. The BoED WG recommended comparing the aetiological proportions between MCEE and IHME and investigating the impact of study adjustments on prevalence estimates.

Methodology: Pathogen prevalence data for ST-ETEC and Shigella were collected from both modelling groups. James Platts-Mills and Sarah Elwood (University of Virginia) conducted a high-level meta-analysis of both groups' age-adjusted data. They also applied IHME data adjustments and examined the impact on prevalence estimates.

Results: The IHME diagnostic test adjustments increase the Shigella mortality estimate by approximately twofold (figure 2A) but do not increase the ST-ETEC estimate (figure 2B); these increases are conservative when compared to the GEMS/MAL-ED re-analyses. The other IHME adjustments have a negligible impact on the estimates (and it is possible that, for example, restricting to studies of hospitalised diarrhoea would yield a different result). Alternative approaches to the diagnostic test adjustment are being considered, but if adopted, would likely further increase the gap between Shigella and ETEC burden for GBD. Differential application of the aetiology proportions to the mortality envelope (national/sub-national by IHME, regional by MCEE) may also lead to differences in the estimates.

Figure 2. Results of the meta-analysis of prevalence estimates and the impact of IHME adjustments for Shigella (A) and ST-ETEC (B), (unpublished, confidential).



Next steps: The analysis is finished and will be published together with other manuscripts as a series of publications related to this work. WHO together with James Platts-Mills and Sarah Elwood will work closely with IHME and MCEE to understand the impact of this analysis on future modelling estimates.

6. Perspectives on findings from IHME, MCEE, and BoED WG/PDVAC members

Hmwe Kyu (IHME) articulated that the analyses undertaken by the BoED are needed and will help to inform future mortality estimates. IHME will continue to work with WHO and modellers who conducted the analyses to understand if and how to incorporate the results into their future estimates. IHME proposed to:

- based on an earlier discussion with the modelling groups, a general consensus was that incorporating CFRs may not be very helpful in improving the estimates. Therefore, IHME won't be incorporating the CFRs but could compare estimated CFRs based on IHME results and the CFRs from the systematic review and investigate potential differences;
- consider incorporating ORs into the PAF calculation, determining a ratio of PCR to conventional detection methods;
- explore the possibility of predicting ORs by country as a function of sociodemographic development.

Robert Black (MCEE) highlighted his recent work with WHO to estimate causes of deaths due to diarrhoea in children and adolescents under 20 years old. MCEE did not publish previous aetiology estimates, as data to inform critical study adjustment such as for the difference in detection methods was missing. The results of the BoED analyses could inform such gaps and facilitate the publishing of future mortality estimates by MCEE. Results of the ORs analysis could be incorporated into future mortality estimates; however, inconsistent patterns of ORs across pathogens and mortality strata need to be fully investigated. MCEE continues to focus on studies in hospitalised patients and aims to calculate regional estimates. The results from the CFR analysis are unlikely to be used, as studies that measure CFRs include inpatient treatment and community interventions, and do not capture the true pathogen mortality.

PDVAC and BoED members (CL, GK, PS) highlighted that these extensive analyses provide more clarity on the data used by both models and improve our understanding of how models are conducted. The analyses help to explain the observed differences in mortality between the two modelling groups. The results should be interpreted with caution, together with wide confidence intervals and a caveat that research sites may not appropriately represent a country in which they are located. The BoED WG should be ready to assess new data that could inform future mortality estimates, such as from the CHAMPS minimally invasive autopsy studies. A set of publications with proposed recommendations for inclusion and exclusion criteria will be an important outcome of this group. Going forward, the group should focus on measuring the full value of vaccines assessment (FVVA), including the impact of enteric pathogens on morbidity, as well as healthcare utilisation.

7. Finalisation of analyses and future steps

The analysis of odds ratios of developing diarrhoea when a pathogen is detected in stool, the study quality analysis, and the meta-analysis of input studies and model adjustments are all completed. The analysis of pathogen-specific CFRs is near completion, and the sensitivity analysis of removing low-quality studies from the IHME analysis is pending but will hopefully be completed this summer.

The model comparison exercise (workstream 4), previously discussed, is on hold and the need for it will be revisited when results from workstreams 1-3 become available. The WHO team will work closely with IHME and MCEE to inform future iterations of U5 mortality estimates, and will share results and accompanying databases from the conducted analyses. Upon completion of workstreams 1-3, WHO proposes to disseminate results through a series of publications. Going forward, WHO and the BoED WG will continue to monitor for additional data to inform models that calculate mortality estimates. The work will also expand to measure the impact of enteric pathogens on morbidity.

8. Discussion and recommendations:

- The outcomes of the BoED WG lead to improved understanding of the data inputs and data processing that inform the U5 mortality estimates, and improve their robustness and credibility;
- Where possible, consider stratifying results to countries and WHO regions; however, as data are scarce, there are large confidence intervals when reporting country-level data;
- Results of all analyses should be represented visually on a map to highlight countries with no data or countries where data quality is low;
- The analyses show that pathogen biology varies between pathogens, and pathogen independent models should be developed to assess the pathogen burden;
- Both the pathogen impact on disease burden as well as a broader impact on diarrhoea should be considered when calculating mortality estimates;
- By the time a vaccine for ETEC or Shigella is developed and licenced, mortality might be a much smaller component of FVVA, and it should be considered together with other components such as morbidity and economic burden;
- Additional PCR, hospital-based, multi-pathogen studies, such as from GPDS, might further inform mortality estimates.

9. The proposed expansion of BoED WG scope to include morbidity assessment

Diarrheal diseases burden estimates have been dominated by childhood deaths, and as a result, public health policy decisions are mainly based on mortality estimates. In addition to mortality, diarrhoea episodes can lead to long-term effects such as wasting, stunting, cognitive impairment, decreased school performance and others. A comprehensive assessment of long-term effects of diarrhoea is challenging, estimates are limited, and methodologies to measure such impact are heterogeneous, often leading to incomparable results. The BoED WG proposes to expand its scope of work to measure the impact of enteric pathogens on morbidity through the following proposed workstreams:

- Conduct a landscape analysis of the available and forthcoming data, and methods used to measure morbidity (variables, metrics, types of tests performed, etc.)
- Examine the evidence for the pathologic pathway leading to long term sequelae of enteric infections and diarrhoea (inflammation biomarkers, EED, stunting, etc.)
- Collaborate with / track the ongoing efforts of the AMR vaccine value attribution framework to incorporate the contribution of AMR, when appropriate
- Identify critical data gaps and propose research studies that may improve understanding, including mining existing data sets from past studies.

- **Output 1:** Identification of data and research gaps to quantify morbidity, recommendations communicated through a publication
- **Output 2:** Assess whether the evidence collected on disease impact and the existing studies/methods to measure morbidity could inform the development of a standardised framework to quantify the burden

The proposed morbidity work would start in September 2020.

Discussion:

- PDVAC agrees with the proposed scope of morbidity work; however, the committee highlighted that the scope needs to inform strategic decisions around vaccine development investment, policy recommendation, and vaccine introduction and use.
- PDVAC recommended to engage early in the process with multiple stakeholders (NITAGs, RITAGs, SAGE, vaccine developers, GAVI) to ensure that results from the proposed workstreams will drive decision making;
- It might be challenging to incorporate estimates of morbidity into current IHME and MCEE models (as they report diarrhoea as a disease and pathogens as risk factors);
- Results of ABCD and CHAIN studies could potentially be used to inform some of the morbidity estimates;
- Consider utilisation of health services, as outpatients, emergency room use and hospitalizations, at a country or regional level, as part of the morbidity assessment;
- An important element of the proposed work is to develop consensus on methodologies to measure the impact of pathogens on morbidity;
- The morbidity caused by AMR pathogens is assumed to be greater than drug susceptible pathogens, the AMR component should be reflected in the morbidity assessment;
- Consider alignment with FVVA, identify elements that are specific to enteric pathogens and the ones that are applicable to a broader group of pathogens.

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	Welcome and introductions			David Kaslow and Martin Friede
15.10 – 15.15	Introduction: session overview & objectives	5’	Summary the purpose of the session and highlight of PDVAC’s 2018 recommendations related to this work	Birgitte Giersing
15.15 – 15.20	Summary of workstreams related to mortality of enteric pathogens	5’	High-level description of all workstreams that investigated the differences in the burden of U5 mortality for enteric pathogens.	Mateusz Hasso-Agopsowicz
15.20 – 15.35	Results of the study grading analysis	10’ + 5’	**For information:** To describe findings of the study quality assessment of studies that were used to calculate mortality estimates	Mateusz Hasso-Agopsowicz
15.35 – 15.50	Analysis of the systematic review of odds ratios	10’+5’	**For information and discussion:** To describe results of the analysis of the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool.	Benjamin Lopman
15.50 – 16.05	Analysis of the systematic review of case fatality rates	10’+5’	**For information and discussion:** To describe results of the analysis of the systematic review of pathogen specific case fatality rates.	Virginia Pitzer
16.05 – 16.20	Results from the meta analysis of input studies	10’+5’	**For information and discussion:** To inform about the results from the meta-analysis of studies used to calculate mortality estimates, and the impact of IHMEs model adjustments on mortality estimates.	James Platts-Mills

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
16.20 – 16.30	Perspectives on findings from the mortality modelling groups	10’	**For information:** To highlight potential implications from the systematic reviews and meta-analysis on future mortality estimates	TBC
16.30 – 16.50	Discussion			Rob to moderate?
16.50 – 16.55	Anticipated outcomes, timelines, next steps	5’	**For information:** To inform on proposed outcome, their timelines, and next steps	Mateusz Hasso
16.55 – 16.15	Expansion of scope to morbidity	10’+10’	**For decision and discussion:** To inform, discuss and agree on the proposed scope of work to measure the impact of enteric infections on morbidity	Ibrahim Khalil
16.15 – 16.45	Closed session	30’		