



World Health Organization Expert Working Group: Recommendations for assessing morbidity associated with enteric pathogens

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ABSTRACT

Background: Diarrhoeal infections are one of the leading causes of child's mortality and morbidity. Vaccines against *Shigella*, enterotoxigenic *E. coli* (ETEC), norovirus and invasive non-typhoidal *Salmonella* are in clinical development, however, their full value in terms of short and long-term health and socio-economic burden needs to be evaluated and communicated, to rationalise investment in vaccine development, and deployment. While estimates of mortality of enteric infections exist, the long-term morbidity estimates are scarce and have not been systematically collected.

Methods: The World Health Organization (WHO) has convened a Burden of Enteric Diseases Morbidity Working Group (BoED MWG) who identified key workstreams needed to characterise the morbidity burden of enteric infections. The group also identified four criteria for the prioritisation of pathogens of which impact on long-term morbidity needs to be assessed.

Results: The BoED MWG suggested to identify and analyse the individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children (workstream 1); to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders (workstream 2); and to conduct a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on health outcomes in adults. The experts prioritised four pathogens for this work: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella* (*dysenteriae*, *flexneri*, *sonnei*).

Conclusions: The proposed work will contribute to improving the understanding of the impact of enteric pathogens on long-term morbidity. The timing of this work is critical as all four pathogens have vaccine candidates in the clinical pipeline and decisions about investments in development, manufacturing or vaccine procurement and use are expected to be made soon.

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1. Introduction

Diarrhoeal infections have killed around 500,000 children under five years of age and resulted in an estimated 45.5 million

disability adjusted life years (DALYs) in 2019 alone, with the majority of the burden occurring in low-income countries [1]. Vaccines are one of the most successful interventions to prevent infections and licensed enteric vaccines against rotavirus, cholera, and typhoid have proven to be safe and effective in preventing diarrhoea episodes and deaths [2]. Vaccines against *Shigella*, enterotoxigenic *E. coli* (ETEC), norovirus and invasive non-typhoidal *Salmonella* are in clinical development. The role of the World Health Organization (WHO) is to consider the use of these vaccines in children under five years old in low- and middle- income countries (LMICs) [3–4]. Other use cases include travellers and military recruits. As such, the full value of vaccines in terms of short and long-term health and socio-economic burden needs to be evaluated and communicated, to rationalise investment in vaccine development, and deployment. The WHO has established an approach to describe the full value of vaccines (FVVA) that are in the early stages of product development [5]. The FVVA approach seeks to understand the perceived burden of disease, to quantify the impact of that burden and the potential benefit of a vaccine, and to drive demand for a vaccine, in particular, from the perspective of LMICs where there is often a lack of epidemiological data to inform decision making and prioritisation of health interventions.

Infections with enteric pathogens, both with and without diarrhoea, can lead to intestinal inflammation and damage, changes in microbiome, nutrient malabsorption, impaired innate and acquired mucosal defences, and worsened clinical presentation of subsequent diarrhoeal infections [6]. Such outcomes can lead to mortality, or potentially to long-term morbidities, such as growth faltering or cognitive impairment, obesity and subsequent metabolic & cardiovascular chronic diseases, as well as socio-economic consequences such as decreased productivity [6]. This extensive burden of enteric infections can have long-lasting effects after the initial infection takes place. To comprehensively assess the FVVA and inform vaccine prioritisation for investment and use, both mortality and morbidity need to be explicitly quantified. Modelling groups such as Institute for Health Metrics and Evaluation (IHME) and Maternal Child Epidemiology Estimation (MCEE) have published mortality estimates for enteric diseases, which were recently reviewed by the WHO [7]. These estimates have decreased over the years and the trend is expected to continue. However, the observed morbidity from enteric infections remains high, and there is a lack of consensus on how to measure, analyse and present such morbidity. As such, the full value of enteric vaccines that impact both mortality and morbidity could be underestimated, compounded by the reality that morbidity is often not fully taken into consideration when decisions about vaccine investments are made.

There is evidence showing an association between diarrhoea episodes and growth faltering. The Global Burden of Disease study suggests that each day of diarrhoea is associated with an average loss in length-for-age Z-score (LAZ) of 0.0033, a weight-for-age Z-score loss of (WAZ) 0.0077, and a weight-for-height Z-score loss (WHZ) of 0.0096. The long-term consequences of undernutrition increase the risk of other infectious diseases and increase the total DALY burden associated with enteric infections by 39% [8]. In a large cohort study (MAL-ED), diarrhoea episodes attributed to bacteria or parasites, and high enteropathogen exposure were associated with decreases in growth [10–11]. Aetiology specific analyses suggest that diarrhoeal episodes caused by *Cryptosporidium*, *Campylobacter jejuni/coli*, *Shigella*, enteroinvasive, enteropathogenic or enterotoxigenic *Escherichia coli*, and norovirus impact short or long-term growth in children, albeit inconsistently [9–11]. In addition, non-diarrhoeal infections with *Shigella*, ETEC, *Campylobacter* and *Giardia lamblia* have been associated with substantial decreases in LAZ [11].

Estimating the impact of enteric infections on growth faltering or cognitive impairment is challenging as data are limited, often poorly represent the regions where burden of enteric infections is high, and there is limited consensus on comparison groups, time-frames, and outcome metrics that should be used to measure such impact. The pathway from having an enteric infection to intestinal damage, malabsorption and impact on growth and cognition contains multiple steps, each with a unique set of definitions, indicators and metrics, which are difficult to harmonise across multiple studies or sites. The assessment of morbidity is further complicated by time-varying confounders, which may bias observational associations. Finally, many of the relevant outcomes are highly multifactorial and occur months or years after the infections, making causal inference for often small associations difficult.

WHO has convened a Burden of Enteric Diseases Morbidity Working Group (BoED MWG) with a remit to better understand the morbidity burden of enteric infections and contribute to the characterisation of the full value of enteric vaccines. This article is a summary report of the discussions of the BoED MWG which took place quarter one and two of 2021. The WG identified key workstreams needed to characterise the morbidity burden of enteric infections and prioritised pathogens for such assessment.

2. Summary of discussion and identification of workstreams

The BoED MWG agreed that the understanding of the full value of enteric vaccines is incomplete and analyses of the impact of enteric pathogens on short- and long-term morbidity are critical to ensure rapid vaccine development and deployment. The potential use of enteric vaccines in the travellers' market in high income countries is an opportunity to accelerate the development of enteric vaccines for later use in LMICs. As such, analyses of the impact of enteric pathogens on adults should be a part of the analyses. The experts agreed that the conceptual pathway of diarrhoea to long-term morbidity is well established, and growth, specifically stunting is the most frequent outcome metric used to assess chronic malnutrition in children.

Previous analyses have explored the association between diarrhoea and growth; however, comprehensive analyses of aetiology specific impact of enteric infections on long-term morbidity are scarce. Studies that measure growth such as MAL-ED and GEMS should be explored for datasets that could be combined and re-analysed using systematic and standardised analyses to inform the morbidity work.

Identification, collection and analysis of confounders should be an integral part of the morbidity analyses. Analyses of data at an individual level can help to understand the effect of confounders on long-term morbidity. Analyses should control for the effect of time, consider specific pathogens, and include time-series analyses. Given the growing evidence that asymptomatic enteric infections are associated with malnutrition and stunting, their impact should be included in the assessment of morbidity. As such, the BoED MWG has proposed three workstreams to better understand the impact of enteric infections on morbidity:

- 1) Workstream 1: identification and analysis of individual level data from historical datasets to estimate the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children.
- 2) Workstream 2: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders.

Table 1
Selection of pathogens for the assessment of morbidity.

Pathogen	In clinical development	Source	Vaccine development feasibility	Evidence that symptomatic infections impact growth or cognition	Evidence that non-diarrhoeal infections impact growth or cognition	Included in the analysis?	Reason(s)
Adenovirus	No	Clinicaltrials.gov	NA	Yes [11]	No	No	* No vaccine in clinical development, * No evidence that non-diarrhoeal infections impact growth or cognition
Aeromonas	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Astrovirus	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
<i>Clostridium Difficile</i>	Yes	internal pipeline	Moderate	No	No	No	* No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
<i>Entamoeba</i>	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Rotavirus	Yes	licensed	High	No	No	No	* A vaccine exists and is used in LMICs * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
<i>Salmonella enteritidis</i>	Yes	internal pipeline	Moderate	No	No	No	* No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
Sapovirus	No	Clinicaltrials.gov	NA	No	No	No	* No vaccine in clinical development, * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
<i>Vibrio cholerae</i>	Yes	licensed	Moderate-High	No	No	No	* A vaccine exists and is used in LMICs * No evidence that symptomatic infections impact growth or cognition * No evidence that non-diarrhoeal infections impact growth or cognition
<i>Cryptosporidium</i>	No	Clinicaltrials.gov	Low[12]	Yes [11,13]	No	No	* No vaccine in clinical development * Low feasibility of vaccine development * No evidence that non-diarrhoeal infections impact growth or cognition
EPEC	No	Clinicaltrials.gov	Low[14,15]	Yes [16]	Yes [17]	No	* No vaccine in clinical development * Low feasibility of vaccine development
<i>Giardia lamblia</i>	No	Clinicaltrials.gov	Low[18-20]	Yes [17]	Yes [11]	No	* No vaccine in clinical development * Low feasibility of vaccine development
EAEC	No	Clinicaltrials.gov	Low	Yes [10,16–17]	Yes [10–11]	No	* No vaccine in clinical development * Low feasibility of vaccine development
<i>Campylobacter jejuni</i>	Yes	internal pipeline	Moderate	Yes [10,16–17]	Yes [10–11]	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition * Evidence that asymptomatic infections impact growth or cognition
ETEC (LT or ST)	Yes	internal pipeline	Moderate-High	Yes [11,16–17]	No	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition

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Table 1 (continued)

Pathogen	In clinical development	Source	Vaccine development feasibility	Evidence that symptomatic infections impact growth or cognition	Evidence that non-diarrhoeal infections impact growth or cognition	Included in the analysis?	Reason(s)
Norovirus G1 or GII	Yes	Clinicaltrials.gov	Moderate	Yes [11,16–17]	No	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition
<i>Shigella</i> (<i>dysenteriae</i> , <i>flexneri</i> , <i>sonnei</i>)	Yes	internal pipeline	Moderate	Yes [11,16–17]	Yes [11]	Yes	* Vaccine candidates in development * Feasibility of producing a vaccine moderate or higher * Evidence that symptomatic infections impact growth or cognition * Evidence that asymptomatic infections impact growth or cognition

- 3) Workstream 3: a systematic review of evidence on the association of aetiology specific diarrhoea with short- and long-term impact on health outcomes in adults.

3. Selection of pathogens for the assessment of morbidity burden

Given the time and workload constraints, the BoED MWG proposed a standardised approach to select pathogens for the assessment of morbidity in children (workstreams 1 and 2). The group identified an initial list of seventeen pathogens (Table 1) for which the mortality burden was previously assessed by IHME or MCEE. A list of the following criteria was identified to prioritise the pathogens for the analyses:

- A. **Active vaccine candidates in the clinical pipeline:** the experts gave preference to pathogens for which there are active candidates in the clinical pipeline as the assessment of morbidity should inform the FVVA and drive decisions about future investment in vaccine development, introduction, and use.
- B. **Feasibility of developing a vaccine:** preference to pathogens for which there is at least moderate feasibility of developing a vaccine as identified by the WHO feasibility assessment and scientific literature. Vaccines for which FVVA is conducted should be biologically feasible, could be developed, and would likely to be licensed and used.
- C. **Evidence of association between symptomatic infections and morbidity:** preference to pathogens for which there is some evidence on the association between symptomatic infections and growth faltering or cognitive outcomes as previous morbidity analyses indicate which pathogens should be analysed in more detail.
- D. **Evidence of an association between non-diarrhoeal infections and morbidity:** preference was given to pathogens for which there is evidence that asymptomatic infections are associated with morbidity as asymptomatic infections are not reflected in the acute burden but might impact on growth faltering and cognitive outcomes.

Based on these criteria, the group has prioritised four pathogens to assess their impact on morbidity in children: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella* (*dysenteriae*, *flexneri*, *sonnei*). The prioritisation process with rationale for exclusion and inclusion is presented in Table 1.

For workstream 3, based on the knowledge of post-infectious sequelae among adults and in alignment with the pathogen list for children, *Campylobacter jejuni* and *Shigella* spp. will be considered and explored for possible association with long-term adult health outcomes globally.

4. Conclusions

There is a need to capture and articulate the full burden of enteric pathogens which are endemic to LMICs and for which vaccine development has a limited commercial attractiveness. For enteric pathogens, there are existing estimates of mortality, however, estimates of morbidity are scarce, and with the exception of data from few cohort studies, have not been systematically evaluated. Analyses that assess the impact of specific enteric pathogens on growth faltering and cognition are lacking. As such, there are major opportunities to analyse individual-level data in existing cohort studies such as MAL-ED, GEMS, VIDA, and identify relevant confounders that may impact the assessment of morbidity (workstream 1). Similarly, there is an opportunity to conduct a systematic review of evidence of the impact of enteric infections on long-term morbidity in children (workstream 2). Lastly, there is a need to assess the evidence of longer-term morbidities in adults, including potential associations with arthritis and functional bowel disorders (workstream 3).

The proposed workstreams should be conducted for at least four pathogens: *Campylobacter jejuni*, ETEC (LT or ST), norovirus (G1 or G2), and *Shigella* (*dysenteriae*, *flexneri*, *sonnei*). All these pathogens have vaccine candidates in clinical pipeline with at least moderate feasibility of vaccine development. As such, decisions about investments in development, manufacturing or vaccine procurement and use are expected to be made soon. There is evidence that symptomatic infections with these pathogens impact growth or cognition. For *Shigella* and *Campylobacter jejuni* there is evidence that asymptomatic infections could impact growth and cognition, further highlighting the need to capture and evaluate morbidity. The specific indicators to evaluate morbidity should be established as part of the analyses and will be guided by the type of data already collected.

The results of the proposed workstreams are expected to be incorporated to the morbidity estimates generated by the modelling groups, and subsequently inform and influence decision making about the development, introduction and use of enteric vaccines. The assessment of morbidity will help funders to decide where to direct their investments; help manufactures to decide which vaccines should be included in their development portfolio;

help international organizations such as Gavi or UNICEF to decide which vaccines to purchase and procure; and help countries to evaluate the role of vaccines in preventing the burden of enteric infections in the context of other interventions.

Once a consensus on the mortality and morbidity burden of enteric pathogens is agreed, additional analyses, beyond the scope of this review, to characterise the full value of vaccines should focus on evaluating the socio-economic impact such as the effect on educational attainment, impact on lifetime productivity and earnings, impact on household costs, poverty, social inequity and economic growth. Research could investigate the impact of morbidity burden on health systems, particularly in LMICs. Additional work could focus on developing a global guidance for metrics and indicators used to measure all components of the pathway from an enteric infection to long-term morbidity, such as environmental enteric dysfunction, malnutrition, growth faltering, and cognition.

5. Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

6. Data statement

Data can be accessed on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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