Capturing the true burden of *Shigella* and ETEC: The way forward

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ABSTRACT

The mortality and morbidity burden estimation of diarrheal diseases (DD), and *Shigella* and Enterotoxigenic *E. Coli* (ETEC) varies among different studies and by the models used for producing these estimates. Understanding the real burden of these important pathogens will guide public health and policy makers to prioritize resources for accelerating interventions against these enteric infections. In addition, long term effects, in the form of growth faltering, cognitive impairment and decreased school performance are important aspects of burden that has not been well captured. Efforts to incorporate these effects and refine their estimation, in the form of Disability Adjusted Life years (DALYs) are very important to inform the burden of diarrheal diseases and *Shigella* and ETEC specifically. The Institute for Health Metrics and Evaluation (IHME) at the University of Washington conducted a workshop at the VASE 2018 meeting to discuss IHME Global Burden of Diseases (GBD) modelling methods for diarrheal diseases, with a focus on ETEC and *Shigella* estimates in relation to other pathogens, including limitations, areas of improvements, and IHME plans for future GBD iterations.

1. Introduction

The IHME team presented about the Global Burden of Disease, Injuries, and Risk Factors study 2016 (GBD 2016 at the VASE 2018 meeting in Mexico City. The GBD is a systematic, which is a scientific effort to quantify the morbidity and mortality due to over 300 causes of death and disability. The workshop discussed the analysis of the global burden of *Shigella* and ETEC diarrhea for each age, sex, geography, and year from 1990 to 2016. The presentation focused on the GBD DD modeling methods, estimates, and reported the GBD 2016 study findings for DD, where diarrhea accounts for more than 1 million deaths and about 4% of the total global disability-adjusted life-years (DALYS) per year across all age groups [1–3]. Although mortality rates from DD have decreased since 1990, diarrhea morbidity remains high, particularly in low income and middle-income countries (LMICs), where access to care, relevant microbiological diagnostics, water quality, and sanitation are poor, and adequate health-care facilities, diagnostics, and treatment interventions are scarce [1,4].

2. Presentation

IHME presented the GBD methodology to estimate *Shigella* and ETEC and the health-loss due to *Shigella* and ETEC diarrhea. The GBD includes incidence, disability-adjusted life-years, and mortality for 195 countries, for each sex, and all ages from 1990 to 2016. Data sources for the analysis of the global burden of *Shigella* and (ETEC) diarrhea included vital registration and verbal autopsy data for all-cause diarrhea mortality, population representative surveys, scientific literature, and health-care utilization data The attributable fraction of diarrhea burden due to *Shigella* and ETEC was modelled using data from the scientific literature. Etiologic attribution to *Shigella* and ETEC also relied on the Global Enteric Multicenter study for informing adjustments to account for diagnostic misclassification and the association between pathogen presence and diarrhea, expressed as odds ratios. Some detail was provided about the counterfactual definition used for diarrheal etiology attribution, including for *Shigella* and ETEC. Some detail was provided about the counterfactual definition used for diarrheal etiology attribution, including for *Shigella* and ETEC. Modeled estimates of the frequency of these pathogens in diarrheal stool samples, by age, sex, year, and geography are combined with the association between the pathogens and diarrhea, represented by odds ratios. We also discussed the methods used to account for diagnostic misclassification of bacterial culture compared to molecular diagnostics. Data availability, covariates, and brief descriptions of modeling strategy were provided. Further details about the modeling methods and GBD estimates for diarrhea and *Shigella* and ETEC are reported in detail elsewhere and including in the recently published manuscript on these pathogens [5]. We next presented on results from the GBD 2016 study [6]. Among all ages, diarrhea was responsible for an estimated 1,655,944 (95% Uncertainty Interval [UI]:

1,244,073–2366,552) deaths among all ages and 445,999 (95% UI: 390,894–504,613) among children younger than 5 years, making it the 8th leading cause of death overall. Diarrhea mortality was geographically concentrated in sub-Saharan Africa and South Asia and among young children and elderly adults. The GBD estimated that *Shigella* was responsible for 212,400 (95% UI 137,000–326,900) deaths among all ages, including 63,700 (95% UI 41,200–93,600) deaths among children younger than 5 years, and that ETEC was responsible for 51,200 (95% UI 26,800–83,100) deaths among all ages and 18,700 (95% UI 9,800–30,700) deaths in children younger than 5 years [5]. This suggests that interventions that prevented *Shigella* diarrhea mortality could avert 14.3% (95% UI 9.6–20.7%) of under-5 diarrhea deaths while interventions to prevent ETEC mortality could avert 4.2% (95% UI 2.2–6.9%) of under-5 diarrhea deaths.

It was suggested in the literature that these infections can also hinder cognitive development, with adverse consequences on school performance and economic status [6–9].

The IHME team also compared GBD estimates with other estimates and highlighted the differences in modeling methods. Many other estimates used a categorical modelling approach, meaning that if a pathogen was present in a diarrheal stool sample, diarrhea was attributed to that pathogen, and used conventional bacterial culture methods for diagnostic detection. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) study 2016 used an attributable fraction methodology [10] and results based on molecular diagnostics. IHME also presented about how the use of real time PCR diagnostics has substantially improved the detection of *Shigella* and ETEC pathogens and, therefore, has changed the fraction of moderate and severe diarrhea cases that are attributable to these pathogens [11,12].

The last section of the presentation focused on extensions of diarrhea burden estimation that are ongoing at IHME including producing estimates of diarrhea burden at a precise geospatial resolution, accounting for some of the health-loss associated with linear growth faltering due to diarrhea [7], evaluating the cost-effectiveness of interventions to prevent diarrhea, and forecasting disease burden from 2016 to 2040 [8].

Several limitations were highlighted for in the interpretation of these results. The estimates of mortality, morbidity, and etiologic attribution for *Shigella* and ETEC are limited by data availability in some age groups, like the neonatal period, and particularly by data sparsity in regions of the world with high diarrhea burden. A list of all GBD 2016 data sources is available for each country at http://ghdx.healthdata.org/gbd-2016/data-input-sources.

The GBD study must produce estimates for every geography, age, sex, and year and so many results reflect the relative amount of certainty around the estimates using uncertainty intervals from posterior distributions. Our hierarchical modelling approach allows to use covariates and "borrow" statistical information across time and geography to generate the best possible estimates. The uncertainty around data sparse areas will be relatively greater than those with better data coverage. There is also a general dearth of data on diarrhea among populations older than 5 years, and although GBD model diarrhea etiologies in these age groups, the odds ratios derived from children 1–4 years old were assumed to be representative in older ages.

This analysis also only accounts for the acute phase of diarrhea in our YLD estimates for the two pathogens. Consequently, our DALYs estimates severely underestimate diarrhea-associated long term sequalae, such as stunting and cognitive impairment [9,10,11]. IHME is planning to conduct more studies in the future as more data is generated to inform these outcomes for *Shigella* and ETEC diarrhea, which will provide better estimates on the comprehensive burden of these pathogens.

3. Discussion

After the presentation by the IHME team, there was a broad discussion about the need for a widespread improvement in the quality and quantity of data; including improving surveillance systems and utilizing standard reporting mechanisms and case definitions.

Many of the experts in the field provided helpful feedback about the areas of improvements for DD burden estimates in general (e.g. estimating asymptomatic enteric infections), and for the 2 pathogens. A suggestion for areas where data don't exist, was not to present estimates for these geographies.

A detailed discussion about the best way to deliver the message about the continuously changing DD burden estimates, especially with the GBD study updates was conducted. The experts attending suggested some strategies to avoid confusion among the field experts, stake holders and policy makers. It was suggested discus the uncertainty intervals and reporting the ranges of estimates produced in the GBD presentations and publications. The experts also suggested to put more emphasis on data sources and clarify the changing estimates as more data are being generated and incorporated in the GBD models.

Producing refined burden estimates for the acute and long term burden of *Shigella* and ETEC was also identified as essential to guide funders and public health officials to make evidence based decisions for the alleviation of DD, with particular attention to the development of effective and attainable vaccine. A special emphasis for how ETEC and *Shigella* burden estimates can guide vaccine development, coverage and regimens was imposed in the discussion.

4. Conclusion

The presented GBD estimates for diarrhea and diarrhea attributable to ETEC and *Shigella* showed that these are two of the leading bacterial causes of diarrhea mortality. The uncertainty in the estimates called for a widespread improvement in the quality and quantity of data, including improved surveillance systems and utilization of standard reporting mechanisms and case definitions. Refined burden estimates for the acute and long-term burden of *Shigella* and ETEC are needed to guide funders and public health officials to make evidence-based decisions for the alleviation of DD, with particular attention to the development of effective and attainable vaccines. Data on the burden of DD caused by *Shigella* and ETEC will help public health officials to identify proper age appropriate vaccination schedules and target regions where the burden of these pathogens is substantial and strengthen the collective understanding that alleviating the burden due to these pathogens is urgently needed.

Conflicts of interest

None.

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