Burden of Disease for Enteric Pathogens.

WHO Product Development for Vaccine Advisory Committee (PDVAC) Consultation, 26-28th June 2019

Holly Prudden, Birgitte Giersing, Mateusz Hasso-Agopsowicz
Recap:

- ETEC remains a priority pathogen in LMICs and PDVAC will continue to advocate for, and support, the development of a vaccine. A key component of this effort should focus on improving the understanding and credibility of BoD estimates.

- Shigella remains a priority with primary goal to develop a safe, effective and affordable vaccines to reduce morbidity and mortality.

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<td>U5 Diarrhea Deaths Due to Pathogens: Shigella:</td>
<td>33,400 (24,900-43,500)</td>
<td>28,000 (17,000-71,000)</td>
<td>99,680 (59,550-161,235)</td>
<td>Unpublished data, expected to show minor revisions in estimates associated with both pathogens.</td>
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<td>ETEC:</td>
<td>23,100 (17,000-30,000)</td>
<td>42,000 (20,000-76,000)</td>
<td>15,960 (44,000-40,300)</td>
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Recommendations:

“To further investigate understanding and credibility of Burden of Disease estimates, through the formation of a joint IVIRAC/PDVAC independent working group to evaluate diarrheal burden models, and particularly to assess the level of uncertainty regarding ETEC mortality estimates.”
Implementation of PD-VAC Recommendations

Formation of Expert Working Group (Summer 2018)

Organisation of Two Day Consultation with Modelling Groups (November 2018)

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Observer: Laura Lamberti (BMGF)

**WHO Secretariat:** Birgitte Giersing (PDVAC sec), Raymond Hutubessy (IVIRAC sec), Holly Prudden, Mateusz Hasso-Agopsowicz
Purpose of Consultation

- To identify common assumptions and major differences between two burden models, focusing on global U5 mortality estimates.
- To identify recommendations/activities that may improve current inputs.
- To identify recommendations/areas for further work to further increase the transparency and understanding of the global U5 mortality estimates.
- To identify aspects that may inform and align future iterations of the models.
- To draft a work plan over the next 12-18 months with the overall aim to better understand the BoD estimates of both groups.
Key Lessons from Consultation

• IHME and MCEE produce different model estimates. This is particularly pronounced with respect to Shigella and ETEC.

• There are 3 broad levels at which differences in methodology may give rise to differences in estimates:
  • Differences in **model structure**
  • Differences in **methodology for processing the data**
  • Differences in **data quality**, inclusion and exclusion criteria
A work plan, with four corresponding workstreams* was formulated by the Working Group and both IHME and MCEE to explore methodological issues that explain the differences in estimates and address data gaps, which would improve overall understanding and quality of the modelling processes:

1. **Data Processing Exercise** – a high level assessment of similarities and differences in study data.

2. **Model Comparison Exercise** – to address structural differences in models.

3. **Data Quality Exercise** – to improve understanding of the data utilised for modelling purposes.

4. **Data Gaps** – to identify and address areas of commonality where additional evidence may improve future estimates.

*Workstreams presented to IVIR-AC committee (March 2019) with endorsement of proposals and importance of this work*
1. Data Processing Exercise

Purpose: A high-level assessment of differences in the studies used by each of the modelling groups.

Step 1: Identify which studies the groups have in common and those that are different.

Step 2: Carry out a meta-analysis of the input data used by both groups (by region) to assess where fundamental differences may occur.
2. Model Comparison Exercise

**Purpose:** To assess the relative differences in model outputs generated by both groups, when a common dataset is applied to both models.

**Method:** We will aim to utilise MCEE U5 data to generate the required outputs.

The relative difference between these estimates is explained by differences in model structure and processing *not by the data used*.
3. Data Quality Exercise

**Purpose:** To grade the quality of the data utilised by both groups using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies, to help inform the standard of data acceptable for estimating future modelling analysis on the burden of enteric disease.

- Studies used by IHME and MCEE
- Grading Criteria (NOS)
  - Selection criteria
  - Exposure criteria
  - Comparability criteria
  - Outcome criteria
  - Additional factors
- Results, to inform a WHO paper
4. Data Gaps

**Purpose:** To generate additional data through systematic reviews to provide the modelling groups with information to strengthen their approach.

**Review 1:** Update Odds Ratios (ORs) for the probability of detecting a pathogen, given diarrhoea. More evidence required on controls.

- OR of presence of pathogen in cases: ++++ (sufficient data)
- OR of presence of pathogen in controls: + (more data required)

**Review 2:** Assumption that case fatality rate (CFR) is the same for all pathogens. More information required to assess this assumption.

- CFR Assumed equal: Shigella, Norovirus, Rota, Salmonella, ETEC, Campylobacter
Work to date

Data Processing Exercise:
- Initial comparison of data to identify differences between MCEE and IHME for six pathogens.
- More thorough review planned and completion of meta-analysis.

Data Quality Exercise:
- Grading analysis proposal generated and agreed upon with Working Group. Next step to share with groups.
- IHME and MCEE studies extracted. Grading analysis to begin, early July.

Model Comparison Exercise:
- Initial model input data compiled and shared.
- U5 data for MCEE model generated and shared.
- Call with IHME scheduled for next steps.

Data Gaps Exercise:
- Criteria defined and agreed upon for systematic reviews.
- Analysis commenced 24/06.

Other Key Outputs:
- Short report for (Nov 2018) meeting consultation completed and shared with meeting attendees.
- Full joint publication on meeting consultation pending submission.
Next steps

- Joint consultation publication submitted (journal tbc) July 2019.
- Publication of two separate systematic reviews.
- Joint publication, outlining proposed future methodology for recommended data used in generating enteric burden of disease estimates, summarising workstreams and key findings.
Thank you