Review and Evidence Synthesis of Diarrhoeal Diseases and Deaths Caused by 14 Pathogens Commonly Transmitted by Food

Terms of Reference

Reference Number: EDTF_001

Purpose
Specific purpose of the work

a. To explore the availability and quality of different existing diarrhoeal envelope estimates (both for cases and deaths) and collaborate with the EDTF, CTF, and WHO to make an informed selection of the best envelope estimates to use, and using the sources selected: compile WHO (Sub-)Regional estimates of the incidence of diarrhoeal disease cases and deaths, by age and sex, and detailing the time for which the estimate was generated and other important variables (see data extraction requirements);
b. To review the literature on national estimates of pathogen-specific incidences of diarrhoea and deaths, for 14 pathogens, and compile these estimates; and
c. To conduct a systematic review of literature, to estimate the pathogen-specific etiology proportions of diarrhoeal cases and deaths for 14 pathogens that are commonly transmitted through foods, for WHO (Sub-)Regions, and by age and sex where possible, and detailing the time for which the estimate was generated, and other important variables (see data extraction requirements).

Background
The first WHO Foodborne Diseases Epidemiology Reference Group (FERG1) estimated the incidence and mortality of diarrhoeal diseases caused by 8 pathogens, up to circa 2012 (Pires et al, 2015). The FERG1 work used two approaches: (1) direct estimation for countries for which national studies of the pathogen-specific incidences of diarrhoeal diseases cases and deaths were published; and (2) for remaining countries, a diarrhoeal envelope approach, where the total estimates of diarrhoeal cases and deaths were apportioned to specific pathogens, using etiology proportions generated from a systematic review. A graphical representation of the FERG1 data inputs is given in the Appendix A, for an example pathogen (Campylobacter). The aim of this new work is to extend the FERG1 work to six additional pathogens, and generate updated estimates that are more current (including more recent evidence) for a larger list of 14 pathogens.

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1 https://www.who.int/groups/foodborne-disease-burden-epidemiology-reference-group-(ferg)
Objectives and specific tasks

PURPOSE A: DIARRHOEAL ENVELOPE SELECTION AND COMPILATION OF ESTIMATES OF DIARRHOEAL DISEASE CASES AND DEATHS

i. Review existing estimates of the incidence of diarrhoea cases and deaths that exist at a global scale (e.g., from IHME, MCEE, PDVAC); and

ii. Assess benefits and limitations of these existing estimates, and collaborate with the EDTF, CTF, and WHO to select which to use as the diarrhoeal disease and mortality envelopes (ensuring we: cover all ages, both sexes, and all WHO (Sub-)Regions; and capture multiple estimates over time if they exist);

iii. Compile global and (Sub-)Regional estimates of the incidence of diarrhoeal disease cases and deaths, from 2000 to the most recent time period, by age and sex, and detailing the time for which the estimate was generated and other important variables (see data extraction requirements).

PURPOSE B: LITERATURE REVIEW OF NATIONAL STUDIES

iv. Review the literature for studies where countries have published national incidence and mortality estimates caused by some or all of 14 pathogens, published between 1990 and the current time period; and

v. From the studies in (d), compile national estimates of the incidence and mortality caused by some or all of 14 pathogens, by age and sex where possible, and detailing the time for which the estimate was generated, and other important variables (see data extraction requirements).

PURPOSE C: SYSTEMATIC REVIEW AND META-ANALYSIS OF ETIOLOGY PROPORTIONS

vi. Conduct a systematic review of studies on the etiology of diarrhoeal diseases in the population (including those included in prior systematic reviews [e.g., Lanata et al, 2013; Pires et al, 2015]), published between 1990 and the current time period; and

vii. From the studies in (f), work in collaboration with the EDTF and CTF to conduct a meta-analysis to estimate study-specific and (Sub-)Regional etiology proportions for the 14 pathogens plus “other”, by age and sex where possible, and detailing the time for which the estimate was generated and other important variables (see data extraction requirements).

Scope of work

The 14 pathogens included for this work are:

• The n=9 pathogens included in the FERG1 review by Pires et al (2015): Campylobacter, Cryptosporidium, EPEC, ETEC, Entamoeba histolytica, Giardia, Salmonella enterica, Shigella, norovirus
• An additional n=2 pathogens included in FERG1: STEC and Vibrio cholerae. While FERG1 used different methods for these two pathogens than the Pires et al approach (see: Ali et al, 2012; Majowicz et al, 2014), FERG2 will apply the same approach to these two as for the n=9 above
• An additional n=3 pathogens that are new for FERG2: Cyclospora, enteroaggregative E. coli, rotavirus

Inclusion and exclusion criteria, in addition to the minimum requirements in the Concept Note:

• FOR ALL PURPOSES: Include: studies/sources from all times and geographic locations; peer-reviewed and grey literature sources including government and institutional reports; all languages.
• PURPOSE A: For estimates of the incidence of diarrhoea cases and deaths, studies should only be considered for inclusion if they provide estimates at a global scale, for all individual WHO (Sub-)Regions.
• PURPOSE B: Studies providing national incidence and mortality estimates should be included if they assess 1 or more of the 14 pathogens, and provide estimates at the population level (e.g., adjusted for any under-reporting)
• PURPOSE C: The systematic review and meta-analysis of etiology proportions should use the following list, to develop inclusion and exclusion criteria that will then be finalized in consultation with the EDTF and the CTF (note: the goal is to ensure study populations represent the general community); the retained covariates should also be documented in the data extraction sheets:

Inclusion:  
• Study conducts laboratory testing on diarrhoeal stool samples for at least 2 pathogens  
• Stool samples come from in-patient (for mortality etiology proportions), out-patient or community (human) populations  
• Study is a prospective assessment of morbidity and/or mortality, including surveillance reports  

Exclusion:  
• Studies focused only on hospital-acquired or antibiotic-associated diarrhoea  
• Studies conducted in specific sub-populations such as travelers, cancer patients (note: studies that did not screen for HIV status, and/or enroll based on HIV status, will be included)  
• Outbreak reports and cross-sectional studies  

Methodological requirements  
• Methods must align with those used by Pires et al (2015), and any deviations from or advancements to these methods must be discussed and agreed with the EDTF and CTF before being implemented.  
• The meta-analysis for PURPOSE C must be done in collaboration with the CTF.  

Requirements for extracted/compiled data and calculated estimates  
The final data extracted from each identified study/source, and the etiology proportions calculated must be captured in a standard spreadsheet (to be provided, see template in Appendix B). For this work, the spreadsheet will capture the following; note, ‘input source’ means the study, report, or other source:  

ALL PURPOSES:  
• Study Design and Study Population Information:  
  o Identification number of the input source  
  o Last name of the first author of input source  
  o Year of publication  
  o Language of publication  
  o DOI of publication, or name of journal/website/etc. if DOI is unavailable  
  o Title of the input source  
  o For the data/values extracted from the input source (note, may require separate rows if multiple different values are extracted from one source, e.g., incidence in children <5 years and incidence in adults):  
    ▪ The starting year of the data (e.g., the beginning of prospective data collection)  
    ▪ The end year of the data  
    ▪ The geographic location from which the data came  
    ▪ The type of population from which the data came: community, outpatient, inpatient  
    ▪ The youngest age of the study population from which the data came  
    ▪ The oldest age of the study population from which the data came  
    ▪ The proportion of males, females, and ‘other’ in the study population from which the data came
PURPOSE A: DIARRHOEAL ENVELOPE SELECTION AND COMPILATION OF ESTIMATES OF DIARRHOEAL DISEASE CASES AND DEATHS

- **Diarrhoecal Disease Cases Incidence Information:**
  - Sample size of the population for which the incidence of diarrhoeal disease (cases) was generated/estimated
  - Numerator for the incidence of diarrhoeal disease, i.e., number of cases of diarrhoeal disease
  - Denominator for the incidence of diarrhoeal disease, i.e., number of individuals at-risk for diarrhoeal disease (may be the same as the sample size)
  - Mean incidence of diarrhoeal disease (cases), in 100,000 person-years
  - Standard error of the mean incidence of diarrhoeal disease
  - Lower confidence level (2.5%) of the mean incidence of diarrhoeal disease
  - Upper confidence level (97.5%) of the mean incidence of diarrhoeal disease
  - If possible, the Monte Carlo simulations from the respective source

- **Diarrhoecal Disease Deaths Incidence Information:**
  - Sample size of the population for which the incidence of diarrhoeal disease deaths was generated/estimated
  - Numerator for the incidence of diarrhoeal disease deaths, i.e., number of deaths from diarrhoeal disease
  - Denominator for the incidence of diarrhoeal disease deaths, i.e., number of individuals at-risk for diarrhoeal disease deaths (may be the same as the sample size)
  - Mean incidence of diarrhoeal disease deaths, in 100,000 person-years
  - Standard error of the mean incidence of diarrhoeal disease deaths
  - Lower confidence level (2.5%) of the mean incidence of diarrhoeal disease deaths
  - Upper confidence level (97.5%) of the mean incidence of diarrhoeal disease deaths
  - If possible, the Monte Carlo simulations from the respective source

PURPOSE B: LITERATURE REVIEW OF NATIONAL STUDIES

- **Information on Pathogens Covered in the Study**
  - Number of pathogens covered
  - List of all pathogens covered
  - Whether the study included an ‘unknown pathogens’ category

- **Information for Each Pathogen Covered**
  - Laboratory methods used to detect the pathogen
  - Genotypes, serotypes identified, etc.
  - **Pathogen-Specific Case Incidence Information:**
    - Sample size of the population for which the incidence of cases was generated/estimated
    - Numerator for the incidence, i.e., number of cases
    - Denominator for the incidence, i.e., number of individuals at-risk (may be the same as the sample size)
    - Mean incidence, in 100,000 person-years
    - Standard error of the mean incidence
    - Lower confidence level (2.5%) of the mean incidence
    - Upper confidence level (97.5%) of the mean incidence
  - **Pathogen-Specific Death Incidence Information:**
    - Sample size of the population for which the incidence of deaths was generated/estimated
    - Numerator for the incidence, i.e., number of deaths
    - Denominator for the incidence, i.e., number of individuals at-risk for (may be the same as the sample size)
    - Mean incidence, in 100,000 person-years
    - Standard error of the mean incidence
    - Lower confidence level (2.5%) of the mean incidence
    - Upper confidence level (97.5%) of the mean incidence
PURPOSE C: SYSTEMATIC REVIEW AND META-ANALYSIS OF ETIOLOGY PROPORTIONS

- **Information on Length of Data Collection:**
  - Whether the study collects at least 12 months of data
  - If the study collects <12 months of data, the months of data collection, and any descriptions of season(s) given (e.g., wet season; summer and fall)

- **Information on Pathogens Covered in the Study**
  - Number of pathogens covered
  - List of all pathogens covered
  - Whether the study included an ‘unknown pathogens’ category

- **Information on the Etiologies, for each Pathogen:**
  - Laboratory methods used to detect the pathogen
  - Genotypes, serotypes identified, etc.
  - The number of samples positive for the pathogen
  - The total number of samples tested for the pathogen

a. **WHO Regions/Sub-Regions:**

  See Concept Note.

**Overall timeline (indicative)**

**Start date:** 30 September 2022  **End date:** March 2023

**Deliverables and timeline for delivery**

Completion of final analysis and feedback report to WHO and FERG. The contractors will deliver a final dataset and report documenting results, to be further analysed and interpreted by the EDTF and CTF. This work will be presented to the WHO and FERG for review, and subject to its review process, prior to finalization of reports and publication(s). It is expected that this review will result in a manuscript for publication in at least one peer review journal. Contractors are to lead the writing process, in close coordination with the EDTF. The publication process will be governed by the existing publication policy, and authorship is subject to the recommendations for defining the role of authors and contributors published by the International Committee of Medical Journal Editors (ICMJE).
Interim deliverables

1. Protocol development and registration
   a. The protocol for the systematic reviews needs to be developed in line with the PRISMA-P guidelines (http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf).
   b. Protocols need to be registered in Prospero, for full transparency (https://www.crd.york.ac.uk/prospero/).

2. Interim meetings with EDTF and CTF

3. Final report
   a. Draft report
   b. Final report

4. Electronic copies of all references from which evidence was extracted (organized for easy use and with source identification number included in the file name)

5. Electronic copies of the final data extraction sheets
   a. Data extraction sheet templates at start of review
   b. Revised data extraction sheets incorporating FERG feedback
   c. Final data extraction sheets containing evidence extracted and estimates calculated

6. For at least the studies in (b) above, flag to the EDTF any that contain additional results on:
   a. duration of diarrhoeal illness (e.g., overall, by pathogen or severity [e.g., mild, moderate, severe]);
   b. sequelae of diarrhoeal illness (e.g., by pathogen);
   c. Stunting as an outcome of either diarrhoea or specific diarrhoeal pathogens; and
   d. Resistance of the diarrhoeal pathogens to antimicrobials.

Final deliverables:

1. Complete final analysis (in a form of a report) to be delivered at the end of the contract period. Report content, quality and style include:
   a. Abstract
   b. Introduction
   c. Methods
   d. Results
   e. Discussion
   f. Conclusion
   g. Annexes

2. Report documenting results in a format of word document, to be delivered at the end of the contract period (July 2024)

3. External journal publication (including authors from the EDTF) as the outcome of the above outputs (2025)

Qualifications, experience, skills and languages

a. Educational qualifications
   The commissioned scientist and/or team under their direction should have:
   • A PhD or equivalent (e.g., DrPH) in epidemiology, public health, or similar discipline
   • Training in the epidemiology of foodborne diarrhoeal diseases, through clinical specialization or academic experience

b. Experience
• 5+ years research experience in the epidemiology of foodborne or diarrhoeal diseases in humans
• Experience estimating the global or regional diarrhoeal disease incidence or mortality, or working with such estimates to generate global burden of disease results;
• Experience conducting systematic reviews and meta-analyses of diarrhoeal disease etiology;
• Experience collaborating with end-knowledge users (e.g., government agencies) throughout the systematic review process, to ensure the type and format of evidence generated by the review are directly useable by the end-user (here, FERG2).

c. Languages and level required:
• Strong communication skills in English, especially in scientific written communication
• Ability to screen and extract data from references in languages other than English, particularly Arabic, Chinese, French, Russian or Spanish, is an asset.

Other requirements
The study team will be selected from the submitted expressions of interest and based on the members’ qualifications and skills (see specifications below). The team should be composed of at least two persons. Geographical and gender diversity is encouraged. The team members will participate in their individual capacity rather than as a representative of their employer. Each member will also need to complete the standard WHO Declaration of Interest form, which will be assessed for conflict of interests. The team leader may be asked to further elaborate the expression of interest in a virtual video meeting with the WHO Secretariat and the EDTF. The final candidates will be selected through a competitive process in accordance with WHO’s policies and procedures.

References


HOW TO APPLY FOR A CALL FOR EXPRESSIONS OF INTEREST

To complete the application the team leader must provide responses to questions explicitly detailed in the application portal linked below. **It is important to have all information prepared prior to applying online, as it is not possible to return to the portal to modify your submission:**

**APPLY HERE:**

Required information:

1) Reference number (found in the Terms of Reference)
2) Contact information from the main focal point only (i.e. Lead Investigator)
3) Cover letter/statement of motivation, including a maximum of 600 words detailing why your team are submitting this Expression of Interest, and why you believe your team is the most suitable to undertake this work. **It is recommended to prepare this in a separate Word document so you can copy and paste text into the application.**
4) Proposed fee for undertaking the work (in USD)
5) Ideal start date and completion dates to undertake the work
6) ONE document (ideally in PDF format) that includes every Curriculum Vitae (CV) of the proposed research team.
7) ONE document (ideally in PDF format) that includes a brief biography of each research team member (max 150 words per person).

Applications close at 17:00 (CET) on 30 September 2022

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