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Enteric *Salmonella* in humans and food in the Middle East and North Africa: protocol of a systematic review

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ABSTRACT

Introduction Non-typhoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. This protocol provides methods that will be used to synthesise available epidemiological data on non-typhoidal enteric *Salmonella* in humans and food in Middle East and North Africa (MENA) region and to characterise the morbidity of human salmonellosis in this region.

Methods and analysis A systematic review will be conducted based on the Cochrane Collaboration handbook and will be reported following the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We will search PubMed, Embase, CAB Direct and Global Health Library (WHO) databases in order to identify relevant reports. Additionally, the literature search will be supplemented by checking references of the included reports and the identified reviews. Furthermore, we will hand-search conference proceedings and Ministry of Health's website of each country of the MENA region. We will use comprehensive search criteria with no time and no language restrictions. We will extract data on report and study characteristics, biological assay characteristics, individuals' demographic characteristics and on primary and secondary outcomes of interest. If appropriate, meta-analysis will be conducted in order to estimate pooled prevalence measures using DerSimonian and Laird random-effects models. We will conduct meta-regression analysis to explore the effect of study-level characteristics as potential sources of heterogeneity.

Ethics and dissemination The results of the systematic review will be disseminated in a peer-reviewed journal and presented at relevant conferences.

Trial registration number The trial registration number is CRD42016046360.

Strengths and limitations of this study

- ► To the best of our knowledge, this is the first systematic review evaluating the epidemiology of non-typhoidal enteric *Salmonella* in humans and food in the countries of the Middle East and North Africa region.
- ► This systematic review will potentially inform policy makers in order to strengthen national foodborne disease surveillance and to improve food safety in this region.
- ► One of our limitations will be probably a high heterogeneity between studies related to sample size, populations, settings, study periods and the use of different biological assays to ascertain the infection.

INTRODUCTION

Non-typhoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. WHO estimated that the annual median number of non-typhoidal salmonellosis was 78.7 million foodborne illnesses with over 59 000 deaths.[1] As for the WHO-defined Eastern Mediterranean Region, the median incidence rate of non-typhoidal salmonellosis was 1610 illnesses with 0.6 death and disability-adjusted life years (DALYs) was 54 per 100 000 persons, whereas the median incidence rate in the WHO-defined African Region is 896 illnesses with 1 death and 89 DALYs per 100 000 persons.[2]

Countries in the Middle East and North Africa (MENA) region share similar heritage, religion and language. However, the socioeconomic status, governance, growth and development and healthcare system in the MENA region differ widely. Although foodborne disease outbreaks have been frequently reported in the MENA region, a rigorous reporting and monitoring system (ie, active surveillance system) is lacking to quantify the incidence/prevalence of foodborne pathogens and disease. Nonetheless, published studies from the MENA region have reported data on foodborne disease morbidity in human populations. Furthermore, data on the prevalence of food contaminants have been revealed in MENA countries. Non-typhoidal *Salmonella* species are a common cause of foodborne disease in the MENA region.[1] Moreover, *Salmonella* has been detected in an array of food products presented to consumers in the region. The number and quality of the studies differ substantially by country. To the best of our knowledge, there has been no published study

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that systematically reviewed, synthetised and assessed the available data on non-typhoidal enteric *Salmonella* in humans and food in the MENA region. Synthetising the data in addition to characterising the morbidity of human salmonellosis in MENA will provide a rational basis for source attribution studies at regional and country level. Additionally, this study will inform policy maker in order to strengthen national foodborne disease surveillance, improve food safety and prioritise food control intervention programs.

OBJECTIVES

The proposed systematic review will identify, synthetise and assess the available data on non-typhoidal enteric *Salmonella* in humans and food in each country of the MENA region. Therefore, our review will address the following questions: (1) What is the non-typhoidal salmonellosis morbidity in human populations in MENA? (2) What is the non-typhoidal *Salmonella* prevalence in food in MENA? (3) What is the distribution of *Salmonella* serotypes in human populations and food?

METHODS AND ANALYSIS

This systematic review protocol was developed based on the Cochrane Collaboration handbook[3] and reported following the statement outlined by Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statements.[4] PRIMSA-P 2015 checklist[5] was completed and can be found in the research checklist.

Inclusion and exclusion criteria

Types of studies

All reports meeting the inclusion criteria will be included if the study sample size is higher than 10. Case reports, case series, expert opinion, reviews, original articles reporting qualitative and experimental studies, editorials, commentaries, letters to editors, author replies and newspaper articles will be excluded.

Type of participants

Included reports are those studying humans and food. Reports will be excluded if the studies were on enteric *Salmonella* in live food-producing or domestic animals as well as in water, fomite, soil or other environments.

Types of exposures

Included reports are those studying non-typhoidal enteric *Salmonella*. These reports need to present studies that used laboratory testing for *Salmonella* ascertainment. More precisely, in humans, the laboratory testing has to be conducted on stool samples; that is, reports of studies based on clinical diagnosis without any laboratory tests on stool to confirm the causative agent will be excluded. Therefore, reports on non-typhoidal enteric *Salmonella* from gastro-intestinal tract infections will be included, while reports on respiratory, urinary tract and bloodstream infections will be excluded. Additionally, studies on non-typhoidal enteric *Salmonella* cultured from cerebrospinal fluid will be excluded. Reports referring to non-typhoidal enteric *Salmonella* infection as *Salmonella* infection or as salmonellosis will be included, whereas those referring to enteric *Salmonella* as typhoidal, paratyphoidal or invasive non-typhoidal *Salmonella* infection (that is not foodborne or cause of gastro-intestinal tract infections) will be excluded.

Types of outcomes

Our primary outcomes are non-typhoidal enteric *Salmonella* morbidity (prevalence), serotype distribution, bacteria attributable mortality and all-cause mortality in human populations, hospitalisation and length of stay in hospital. Our secondary outcomes are enteric *Salmonella* prevalence and serotype distribution in food.

Data sources and search strategy

Our systematic review will be conducted based on the Cochrane Collaboration handbook[3] and will be reported following the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We will search PubMed,[6] Embase,[7] CAB Direct[8] and Global Health Library (WHO)[9] databases in order to identify further relevant reports (online supplementary file 1). In addition, the literature search will be supplemented by checking references of the included reports and the identified reviews. Furthermore, we will hand-search conference proceedings and Ministry of Health's website of each country of the MENA region. We will use comprehensive search criteria with no time and no language restrictions. We will construct our search criteria using Boolean logic (OR and AND) to combine Medical Subject Headings (MeSH) terms and text words. Key search terms will include countries' names, MENA populations' names and *Salmonella*. We will use WHO/Eastern Mediterranean Region (EMR)[10] definition of MENA region and we will complement this list with four countries whose official languages are Arabic[11] and that are cited in other definitions of MENA.[12–14] The reviewer team does not speak the official language of Cyprus[11] or the media of instruction in its universities and colleges[15]; this will prevent us to identify grey literature such as reports from the Ministry of Health, journal articles and conference abstracts published in these languages. As such, we decide to exclude this country. Our systematic review will include 24 countries, namely: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Mauritania, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates and Yemen. The selected MENA countries have a total population of more than 680 million people.[16]

Study records

Selection process

Identified references will be imported into a reference manager (Endnote[17]) where duplicate reports will be excluded. The title and abstract screening for relevance, followed by the full-text screening of the unique reports,

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will be conducted by KC. This multi-level screening process will be checked by WA. Any disagreements will be resolved by discussion and consensus. Non-eligible reports will be excluded, and the reasons for their exclusion will be recorded.

Data collection process

A piloted standardised form developed in Microsoft Excel 2010[18] by KC and WA will be used for the extraction step. Extraction of relevant data will be done by KC, and 25% of the data will be checked for correctness by WA.

Data items

We will extract data on report characteristics (authors, year of publication, title, etc), study characteristics (year of data collection, study site and design, sampling methodology, prevalence, number of positive cases, sample size, etc), biological assay characteristics, individuals' demographic characteristics (age, gender, etc) and on primary and secondary outcomes of interest.

Risk of bias in individual studies

Based on the Cochrane approach,[3] the risk of bias (ROB) assessment will be conducted at both the study level and the outcome level. Each study will be classified as having a low, high or unclear ROB in each of the three quality domains, namely, sampling methodology, infection ascertainment and response rate. An ROB will be considered low if these three quality domains are probability based, ascertainment by biological assays or response rate is≥80%, respectively. At outcome level, a minimum sample size will be calculated using exact binomial CI formula[19] in order to differentiate outcome measures with good precision. Sample size of studies considered as having good precision should be equal or higher than the minimum sample size defined in this protocol.

Data synthesis

We will report our systematic review following Preferred Reporting Items for PRISMA 2009 statements[20] and PRISMA for Abstracts Checklist.[21] We will qualitatively synthesise the identified data on non-typhoidal enteric *Salmonella* in humans and food. These data will be stratified by country and according to the clinical status of the study populations:

1. Non-clinical populations in community settings: healthy populations, mainly food workers
2. Clinical populations: patients with diarrhoea due to gastro-intestinal pathogenic microbes

In addition, a third stratum will be created for the food category. According to the diversity of the identified population subgroups, we will decide if we also need to create subcategories in each stratum.

If data are appropriate for quantitative synthesis, data analyses will be conducted in R V.3.1.1[22] using the *meta*[23] and *metafor*[24] packages. Using meta-analysis, we aim to estimate pooled prevalence of *Salmonella* in food (stratified by category: poultry, beef and seafood, etc) and in human (stratified by type of population). Outcome measures will be pooled in all strata with at least three outcome measures included. Meta-regression will be used in order to assess heterogeneity across studies[3] related to sample size, populations, settings, study periods and the use of different biological assays to ascertain the infection. Additionally, we will conduct sensitivity analysis restricted to studies at low ROB in order to explore the impact of high ROB study measures on the pooled estimates.

Meta-bias

Regarding meta-bias assessment, we will use funnel plots in order to explore small-study effect on the pooled estimates.[25] Traditional funnel plots (log (odds proportion) vs 1/SE) are inaccurate for meta-analysis of proportion studies. Therefore, we will create funnel plots of log (odds proportion) against sample size.[26] In order to test the asymmetry of the funnel, we will perform Egger test,[25] which is based on SE, as well as Peter test, which is based on sample size.[26 27]

Confidence in cumulative evidence

We will use a narrative justification for the quality of the evidence at the country level. We will consider the quality of evidence being better in a country if at least one country-level study was conducted. This country-level study should have used standard methodology including probability-based sampling. Thus, we will categorise countries as having:

- Poor evidence: poor quality of the outcome measures
- Limited evidence: the number of outcome measures is small but of reasonable quality
- Good evidence: the number of outcome measures is small but with good quality
- Conclusive evidence: enough outcome measures with good quality

DISCUSSION

To the best of our knowledge, this systematic review will be the first attempt to synthetise available data on non-typhoidal enteric *Salmonella* in humans and food in the countries of the MENA region and to characterise the morbidity of human salmonellosis. This work will enable us to identify key pathogen control points that should be reinforced and those that need to be further assessed through country-level studies. Ultimately, this systematic review will provide rational basis for source attribution studies at both regional and country levels.[28] Additionally, this study will inform policy maker actions in order to strengthen national foodborne disease surveillance and to improve food safety and public health in MENA.

Contributors KC and WA contributed to the conception of the study. The manuscript protocol was drafted by KC and revised by WA. The search strategy was developed and will be conducted by both authors who will also screen the potential reports, extract data, assess the risk of bias and perform the data synthesis. Both authors approved the publication of the current protocol.

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