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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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5 6	1	Enteric Salmonella in humans and food in the Middle East and North Africa:
7 8	2	Protocol of a systematic review
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### 1 Abstract

### 2 Introduction

3 Nontyphoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. This

- 4 protocol provides methods that will be used to synthesize available epidemiological data on nontyphoidal
- 5 enteric *Salmonella* in humans and food in Middle East and North Africa (MENA) region; and to
- 6 characterize the morbidity of human salmonellosis in this region.

# 7 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 PRISMA 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. 

- 19 Ethics and dissemination
- 20 The results of the systematic review will be disseminated in a peer-reviewed journal and presented at21 relevant conferences.
- 22 Trial registration number
- CRD42016046360
- 24 Keywords
- 25 Enteric Salmonella, Middle East and North Africa

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2 3 4	1	Strengths and limitations of this study
5 6	2	• To the best of our knowledge, this is the first systematic review evaluating the epidemiology of
7 8	3	nontyphoidal enteric Salmonella in humans and food in the countries of the Middle East and
9	4	North Africa region.
10 11	5	• This systematic review will potentially inform policy makers in order to strengthen national
12 13	6	foodborne disease surveillance and to improve food safety in this region.
14 15	7	• One of our limitations will be probably a high heterogeneity between studies related to sample
16	8	size, populations, settings, study periods, and the use of different biological assays to ascertain the
17 18	9	size, populations, settings, study periods, and the use of different biological assays to ascertain the infection.
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### 1 Introduction

Nontyphoidal Salmonella is considered one of the leading causes of foodborne disease worldwide. The World Health Organization (WHO) estimated that the annual median number of nontyphoidal salmonellosis was 78.7 million foodborne illnesses with over 59 thousand deaths<sup>1</sup>. As for the WHO defined Eastern Mediterranean Region, the median incidence rate of nontyphoidal salmonellosis was 1,610 illnesses with 0.6 death, and 54 disability adjusted life years (DALYS) 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<sup>2</sup>. In the United States alone, an estimated 1.03 million illnesses, 19,500 hospitalizations, and 378 deaths are caused by nontyphoidal Salmonella annually<sup>3</sup>. 

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 health care system in MENA region differ widely. Although foodborne disease outbreaks have been frequently reported in MENA region, a rigorous reporting and monitoring system (i.e., 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. Nontyphoidal *Salmonella* species are common cause of foodborne disease in the MENA region<sup>1</sup>. 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 that systematically reviewed, synthetized, and assessed the available data on nontyphoidal enteric Salmonella in humans and food in the MENA region. Synthetizing the data in addition to characterizing the morbidity of human salmonellosis in MENA will provide a rational basis for sources 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 prioritize food control intervention programs.

### **Objectives**

The proposed systematic review will identify, synthetize, and assess the available data on nontyphoidal
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 nontyphoidal salmonellosis morbidity in human
populations in MENA?, 2) What is the nontyphoidal *Salmonella* prevalence in food in MENA?, 3) What
is the distribution of *Salmonella* serotypes in human populations and food?

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# Methods and analysis This systematic review protocol was developed based on the Cochrane Collaboration handbook <sup>4</sup> and reported following the statement outlined by Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P) 2015 statements <sup>5</sup>. PRIMSA-P 2015 checklist <sup>6</sup> was completed and can be found in Table 1. Inclusion and exclusion criteria

# 7 *Types of studies*

All reports meeting the inclusion criteria will be included if the study sample size is higher than ten. 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.

# 12 *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.

# 16 *Types of exposures*

Included reports are those studying nontyphoidal enteric Salmonella. These reports need to present studies 17 18 that used laboratory testing for Salmonella ascertainment. More precisely, in humans, the laboratory 19 testing have to be conducted on stool samples; i.e., reports of studies based on clinical diagnosis without 20 any laboratory tests on stool to confirm the causative agent will be excluded. Therefore, reports on 21 nontyphoidal 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 22 23 nontyphoidal enteric Salmonella cultured from cerebrospinal fluid will be excluded. Reports referring to 24 nontyphoidal enteric Salmonella infection as Salmonella infection or as salmonellosis will be included; whereas, those referring to enteric Salmonella as typhoidal, paratyphoidal, or invasive nontyphoidal 25 26 Salmonella infection (that is not foodborne or cause of gastro-intestinal tract infections) will be excluded.

# 27 Types of outcomes

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

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1 Data sources and search strategy

Our systematic review will be conducted based on the Cochrane Collaboration handbook <sup>4</sup> 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<sup>7</sup>, Embase<sup>8</sup>, CAB Direct<sup>9</sup>, and Global health Library (WHO)<sup>10</sup> databases in order to identify further relevant reports. 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/EMR<sup>11</sup> definition of MENA region and we will complement this list with four countries whose official languages are Arabic<sup>12</sup> and that are cited in other definitions of MENA<sup>13-15</sup>. The reviewer team do not speak the official language of Cyprus <sup>12</sup> nor the media of instruction in its Universities and Colleges <sup>16</sup>; this will prevent us to identify grey literature such as reports from the ministry of health, journal articles and conference abstract 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  $^{17}$ . 

### 21 Study records

### 22 Selection process

Identified references will be imported into a reference manager (Endnote <sup>18</sup>) where duplicate reports will be excluded. The title and abstract screening for relevance, followed by the full-text screening of the unique reports 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.

# 28 Data collection process

A piloted standardized form developed in Microsoft Excel 2010<sup>19</sup> 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.

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2 3		
3 4	1	Data items
5	2	We will extract data on report characteristics (authors, year of publication, title, among others), study
6 7	3	characteristics (year of data collection, study site and design, sampling methodology, prevalence, number
8 9	4	of positive cases, sample size, among others), biological assay characteristics, individuals' demographic
9 10 11	5	characteristics (age, gender, among others), and on primary and secondary outcomes of interest.
12 13	6	Risk of bias in individual studies
14	7	Based on the Cochrane approach <sup>4</sup> , the risk of bias (ROB) assessment will be conducted at both the study-
15 16	8	level and the outcome-level. Each study will be classified as having a low, high, or unclear ROB in each
17	9	of the three quality domains, namely sampling methodology, infection ascertainment, and response rate.
18 19	10	A ROB will be considered low if these three quality domains are probability-based, ascertainment by
20 21	11	biological assays, or response rate is $\geq$ 80%, respectively. At outcome-level, a minimum sample size will
22	12	be calculated using exact binomial confidence interval formula <sup>20</sup> in order to differentiate outcome
23 24	13	measures with good precision. Sample size of studies considered as having good precision should be
25 26 27	14	equal or higher than the minimum sample size defined in this protocol.
27 28 29 30 31	15	Data synthesis
	16	We will report our systematic review following Preferred Reporting Items for PRISMA 2009 statements
	17	<sup>21</sup> and PRISMA for Abstracts Checklist <sup>22</sup> . We will qualitatively synthesize the identified data on
32 33	18	nontyphoidal enteric Salmonella in humans and food. These data will be stratified by country and
34 35	19	according to the clinical status of the study populations:
36 37	20	1- Non-clinical populations in community settings: healthy populations, mainly food workers
38 39 40	21	2- Clinical populations: patients with diarrhea due to gastrointestinal pathogenic microbes
41	22	In addition, a third stratum will be created for the food category. According to the diversity of the
42 43 44	23	identified population subgroups, we will decide if we also need to create subcategories in each stratum.
45	24	If data are appropriate for quantitative synthesis, data analyses will be conducted in R v.3.1.1. <sup>23</sup> using the
46 47	25	meta <sup>24</sup> and metafor <sup>25</sup> packages. Using meta-analysis, we aim to estimate pooled prevalence of
48 49	26	Salmonella in food (stratified by category: poultry, beef, and seafood, among others) and in human
50	27	(stratified by type of population). Outcome measures will be pooled in all strata with at least three
51 52	28	outcome measures included. Meta-regression will be used in order to assess heterogeneity across studies <sup>4</sup>
53	29	related to sample size, populations, settings, study periods, and the use of different biological assays to
54 55	30	ascertain the infection. Additionally, we will conduct sensitivity analysis restricted to studies at low ROB
56 57 58	31	in order to explore the impact of high ROB study measures on the pooled estimates.
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4 5	2	Meta-bias
6 7	3	Regarding meta-bias assessment, we will use funnel plots in order to explore small-study effect on the
8	4	pooled estimates <sup>26</sup> . Traditional funnel plots (log (odds proportion) vs. 1/standard error) are inaccurate for
9 10	5	meta-analysis of proportion studies. Therefore, we will create funnel plots of log (odds proportion)
11 12	6	against sample size <sup>27</sup> . In order to test the asymmetry of the funnel, we will perform Egger test <sup>26</sup> that is
13 14	7	based on standard error as well as Peter test which is based on sample size <sup>27 28</sup> .
15 16	8	Confidence in cumulative evidence
17	9	We will use a narrative justification for the quality of the evidence at the country-level. We will consider
18 19	10	the quality of evidence being better in a country if at least one country-level study was conducted. This
20 21	11	country-level study should have used standard methodology including probability-based sampling. Thus,
22 23	12	we will categorize countries as having:
24 25	13	- No evidence: no data identified
26	14	- Poor evidence: poor quality of the outcome measures
27 28	15	- Limited evidence: the number of outcome measures is small but of reasonable quality
29 30	16	- Good evidence: the number of outcome measures is small but with good quality
31 32	17	- Conclusive evidence: enough outcome measures with good quality
33 34	18	Discussion
35 36	19	To the best of our knowledge, this systematic review will be the first attempt to synthetize available data
37	20	on nontyphoidal enteric Salmonella in humans and food in the countries of the MENA region; and to
38 39	21	characterize the morbidity of human salmonellosis. This work will enable us to identify key pathogen
40 41	22	control points that should be reinforced and those that need to be further assessed through country-level
42	23	studies. Ultimately, this systematic review will provide rational basis for sources attribution studies at
43 44	24	both regional and country levels. Additionally, this study will inform policy maker actions in order to
45 46	25	strengthen national foodborne disease surveillance and to improve food safety and public health in
47	26	MENA.
48 49 50	27	Ethics and dissemination
51	28	Ethical approval will not be needed as in this systematic review, data used will not be individual patient
52 53	29	data. Therefore, there will be no concerns about privacy. The findings will be disseminated via
54 55	30	publication of a manuscript in a peer-reviewed journal and presented at relevant conferences.

# Author contributions:

2 KC and WA contributed to the conception of the study. The manuscript protocol was drafted by KC and

3 revised by WA. The search strategy was developed and will be conducted by both authors who will also

4 screen the potential reports, extract data, assess the risk of bias and perform the data synthesis. Both

5 authors approved the publication of the current protocol.

### Funding statement

7 This research received no specific grant from any funding agency in the public, commercial, or not-for-8 profit sectors'.

Section and topic	Item N <sub>0</sub>	Checklist items	page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify	Not applicable
Registration	2	If registered, provide the name of the registry (such PROSPERO) and registration number	1
Authors:			1
Contact	3a	Provide name, institutional, e-mail address of all protocol authors, provide physical mailing address of the corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identity the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), if any, in developing the protocol	9
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		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic databases, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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Risk of bias in individual studies	141	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's $\tau$ )	
	15c	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta- regression)	
		15d If quantitative synthesis is not appropriate, describe the type of summary planned	
	15d		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8
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Table 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

Section and topic	Item N <sub>0</sub>	Checklist items	page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify	Not applicabl
Registration Authors:	2	If registered, provide the name of the registry (such PROSPERO) and registration number	1 1
Contact	3a	Provide name, institutional, e-mail address of all protocol authors, provide physical mailing address of the corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identity the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise state plan for documenting important protocol amendments	Not applicabl
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), if any, in developing the protocol	9
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic databases, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies ( such as two independent reviewers)	6
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Data collection process	11c	through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis) Describe planned method of extracting data from reports (such as piloting forms, done	6
		independently, in duplicate), any processes for obtaining and confirming data from investigators	, in the second s
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources),	7
		any pre-planned data assumptions and simplifications	
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of main and	5
prioritization		Additional outcomes, with rationale	
Risk of bias in	141	Describe anticipated methods for assessing risk of bias of individual studies, including whether	7
individual studies		this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
-	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration	
		of consistency (such as I2, Kendall's $\tau$ )	
	15c	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta- regression)	
	15d	15d If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies,	8
Confidence in	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8
cumulative evidence			
		selective reporting within studies) Describe how the strength of the body of evidence will be assessed (such as GRADE)	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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# **BMJ Open**

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

Journal:	BMJ Open
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Complete List of Authors:	Chaabna, Karima; Weill Cornell Medical College – Qatar, Infectious Disease Epidemiology Group; Weill Cornell Medicine, Department of Healthcare Policy and Research Alali, Walid; College of Public Health, Hamad bin Khalifa University
<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Enteric Salmonella, Middle East and North Africa, Food born disease



1 2		
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5 6	1	Enteric Salmonella in humans and food in the Middle East and North Africa:
7 8	2	Protocol of a systematic review
9 10	3	Karima Chaabna <sup>1,2*</sup> and Walid Alali <sup>3</sup>
11 12	4	
13 14	5	
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17	7	Doha, Qatar
18 19 20	8 9	2 Department of Healthcare Policy and Research, Weill Cornell Medical College, Cornell University, New York, USA
21 22	10	3 College of Public Health, Hamad bin Khalifa University, Doha, Qatar
23 24 25	11	Karima Chaabna's email: chaabnak.epi@gmail.com
25 26 27	12	Walid Alali <sup>°</sup> s email: walali@qf.org.qa
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38 39 40	18	Registration: CRD42016046360
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### 1 Abstract

### 2 Introduction

3 Nontyphoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. This

- 4 protocol provides methods that will be used to synthesize available epidemiological data on nontyphoidal
- 5 enteric *Salmonella* in humans and food in Middle East and North Africa (MENA) region; and to
- 6 characterize the morbidity of human salmonellosis in this region.

# 7 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 PRISMA 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. 

- 19 Ethics and dissemination
- 20 The results of the systematic review will be disseminated in a peer-reviewed journal and presented at21 relevant conferences.
- 22 Trial registration number
- CRD42016046360
- 24 Keywords
- 25 Enteric Salmonella, Middle East and North Africa

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1		
2 3 4	1	Strengths and limitations of this study
5 6	2	• To the best of our knowledge, this is the first systematic review evaluating the epidemiology of
7 8	3	nontyphoidal enteric Salmonella in humans and food in the countries of the Middle East and
9	4	North Africa region.
10 11	5	• This systematic review will potentially inform policy makers in order to strengthen national
12 13	6	foodborne disease surveillance and to improve food safety in this region.
14 15	7	• One of our limitations will be probably a high heterogeneity between studies related to sample
16	8	size, populations, settings, study periods, and the use of different biological assays to ascertain the
17 18	9	size, populations, settings, study periods, and the use of different biological assays to ascertain the infection.
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### 1 Introduction

Nontyphoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. The
World Health Organization (WHO) estimated that the annual median number of nontyphoidal
salmonellosis was 78.7 million foodborne illnesses with over 59 thousand deaths <sup>1</sup>. As for the WHO
defined Eastern Mediterranean Region, the median incidence rate of nontyphoidal salmonellosis was
1,610 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<sup>2</sup>.

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 health care system in MENA region differ widely. Although foodborne disease outbreaks have been frequently reported in MENA region, a rigorous reporting and monitoring system (i.e., 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. Nontyphoidal *Salmonella* species are common cause of foodborne disease in the MENA region<sup>1</sup>. 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 that systematically reviewed, synthetized, and assessed the available data on nontyphoidal enteric Salmonella in humans and food in the MENA region. Synthetizing the data in addition to characterizing 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 prioritize food control intervention programs.

# **Objectives**

The proposed systematic review will identify, synthetize, and assess the available data on nontyphoidal
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 nontyphoidal salmonellosis morbidity in human
populations in MENA?, 2) What is the nontyphoidal *Salmonella* prevalence in food in MENA?, 3) What
is the distribution of *Salmonella* serotypes in human populations and food?

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1	Methods and analysis
2	This systematic review protocol was developed based on the Cochrane Collaboration handbook <sup>3</sup> and
3	reported following the statement outlined by Preferred Reporting Items for Systematic Review and Meta-
4	Analysis Protocols (PRISMA-P) 2015 statements <sup>4</sup> . PRIMSA-P 2015 checklist <sup>5</sup> was completed and can
5	be found in Table 1.
6	Inclusion and exclusion criteria
7	Types of studies
8	All reports meeting the inclusion criteria will be included if the study sample size is higher than ten. Case
9	reports, case series, expert opinion, reviews, original articles reporting qualitative and experimental
10	studies, editorials, commentaries, letters to editors, author replies, and newspaper articles will be
11	excluded.
12	Type of participants
13	Included reports are those studying humans and food. Reports will be excluded if the studies were on
14	enteric <i>Salmonella</i> in live food producing or domestic animals as well as in water, fomite, soil, or other
15	environments.
16	Types of exposures
17	Included reports are those studying nontyphoidal enteric Salmonella. These reports need to present studies
18	that used laboratory testing for Salmonella ascertainment. More precisely, in humans, the laboratory
19	testing have to be conducted on stool samples; i.e., reports of studies based on clinical diagnosis without
20	any laboratory tests on stool to confirm the causative agent will be excluded. Therefore, reports on
21	nontyphoidal enteric Salmonella from gastro-intestinal tract infections will be included; while reports on
22	respiratory, urinary tract, and bloodstream infections will be excluded. Additionally, studies on
23	nontyphoidal enteric Salmonella cultured from cerebrospinal fluid will be excluded. Reports referring to
24	nontyphoidal enteric Salmonella infection as Salmonella infection or as salmonellosis will be included;
25	whereas, those referring to enteric <i>Salmonella</i> as typhoidal, paratyphoidal, or invasive nontyphoidal
26	Salmonella infection (that is not foodborne or cause of gastro-intestinal tract infections) will be excluded.
27	Types of outcomes
28	Our primary outcomes are nontyphoidal enteric Salmonella morbidity (prevalence), serotype distribution,
29	bacteria attributable mortality and all-cause mortality in human populations, hospitalization, and length of
30	stay in hospital. Our secondary outcomes are enteric Salmonella prevalence and serotype distribution in
31	food.
	5
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Our systematic review will be conducted based on the Cochrane Collaboration handbook<sup>3</sup> 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<sup>6</sup>, Embase<sup>7</sup>, CAB Direct<sup>8</sup>, and Global health Library (WHO)<sup>9</sup> databases in order to identify further relevant reports. 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/EMR<sup>10</sup> definition of MENA region and we will complement this list with four countries whose official languages are Arabic<sup>11</sup> and that are cited in other definitions of MENA<sup>12-14</sup>. The reviewer team do not speak the official language of Cyprus<sup>11</sup> nor the media of instruction in its Universities and Colleges <sup>15</sup>; this will prevent us to identify grey literature such as reports from the ministry of health, journal articles and conference abstract 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 million people<sup>16</sup>. 

### 21 Study records

### 22 Selection process

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

# 28 Data collection process

A piloted standardized form developed in Microsoft Excel 2010<sup>18</sup> 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.

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2		
2 3 4 5 6 7	1	Data items
5	2	We will extract data on report characteristics (authors, year of publication, title, among others), study
6 7	3	characteristics (year of data collection, study site and design, sampling methodology, prevalence, number
B 9	4	of positive cases, sample size, among others), biological assay characteristics, individuals' demographic
9 10 11	5	characteristics (age, gender, among others), and on primary and secondary outcomes of interest.
12 13	6	Risk of bias in individual studies
14	7	Based on the Cochrane approach <sup>3</sup> , the risk of bias (ROB) assessment will be conducted at both the study-
15 16	8	level and the outcome-level. Each study will be classified as having a low, high, or unclear ROB in each
17	9	of the three quality domains, namely sampling methodology, infection ascertainment, and response rate.
18 19	10	A ROB will be considered low if these three quality domains are probability-based, ascertainment by
20	11	biological assays, or response rate is $\geq$ 80%, respectively. At outcome-level, a minimum sample size will
20 21 22 23	12	be calculated using exact binomial confidence interval formula <sup>19</sup> in order to differentiate outcome
23 24	13	measures with good precision. Sample size of studies considered as having good precision should be
24 25 26 27	14	equal or higher than the minimum sample size defined in this protocol.
28	15	Data synthesis
29 30	16	We will report our systematic review following Preferred Reporting Items for PRISMA 2009 statements
31	17	<sup>20</sup> and PRISMA for Abstracts Checklist <sup>21</sup> . We will qualitatively synthesize the identified data on
32 33	18	nontyphoidal enteric Salmonella in humans and food. These data will be stratified by country and
31 32 33 34 35	19	according to the clinical status of the study populations:
36 37	20	1- Non-clinical populations in community settings: healthy populations, mainly food workers
38 39	21	2- Clinical populations: patients with diarrhea due to gastrointestinal pathogenic microbes
40 41	22	In addition, a third stratum will be created for the food category. According to the diversity of the
42 43 44	23	identified population subgroups, we will decide if we also need to create subcategories in each stratum.
45	24	If data are appropriate for quantitative synthesis, data analyses will be conducted in R v.3.1.1. <sup>22</sup> using the
46 47	25	meta <sup>23</sup> and metafor <sup>24</sup> packages. Using meta-analysis, we aim to estimate pooled prevalence of
48 49	26	Salmonella in food (stratified by category: poultry, beef, and seafood, among others) and in human
49 50	27	(stratified by type of population). Outcome measures will be pooled in all strata with at least three
	28	outcome measures included. Meta-regression will be used in order to assess heterogeneity across studies <sup>3</sup>
51 52 53 54 55	29	related to sample size, populations, settings, study periods, and the use of different biological assays to
54 55	30	ascertain the infection. Additionally, we will conduct sensitivity analysis restricted to studies at low ROB
56 57 58 59	31	in order to explore the impact of high ROB study measures on the pooled estimates.
59 60		7

- Meta-bias Regarding meta-bias assessment, we will use funnel plots in order to explore small-study effect on the pooled estimates <sup>25</sup>. Traditional funnel plots (log (odds proportion) vs. 1/standard error) are inaccurate for meta-analysis of proportion studies. Therefore, we will create funnel plots of log (odds proportion) against sample size <sup>26</sup>. In order to test the asymmetry of the funnel, we will perform Egger test <sup>25</sup> that is based on standard error as well as Peter test which is based on sample size <sup>26 27</sup>. 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 categorize countries as having: \_ No evidence: no data identified 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 synthetize available data on nontyphoidal enteric Salmonella in humans and food in the countries of the MENA region; and to characterize 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 <sup>28</sup>. 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. **Ethics and dissemination** Ethical approval will not be needed as in this systematic review, data used will not be individual patient data. Therefore, there will be no concerns about privacy. The findings will be disseminated via publication of a manuscript in a peer-reviewed journal and presented at relevant conferences.

# Author contributions:

2 KC and WA contributed to the conception of the study. The manuscript protocol was drafted by KC and

3 revised by WA. The search strategy was developed and will be conducted by both authors who will also

4 screen the potential reports, extract data, assess the risk of bias and perform the data synthesis. Both

5 authors approved the publication of the current protocol.

### Funding statement

7 This research received no specific grant from any funding agency in the public, commercial, or not-for-8 profit sectors'.

Section and topic	Item N <sub>0</sub>	Checklist items	page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify	Not applicable
Registration	2	If registered, provide the name of the registry (such PROSPERO) and registration number	1
Authors:			1
Contact	3a	Provide name, institutional, e-mail address of all protocol authors, provide physical mailing address of the corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identity the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), if any, in developing the protocol	9
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Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
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Search strategy	10	Present draft of search strategy to be used for at least one electronic databases, including planned limits, such that it could be repeated	6
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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
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Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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Risk of bias in individual studies	141	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's $\tau$ )	
	15c	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta- regression)	
		15d If quantitative synthesis is not appropriate, describe the type of summary planned	
	15d		
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8
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10	6	Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and
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12 13	8	doi: 10.1371/journal.pmed.1001921
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16	11	4. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review
17 18	12	and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews
19	13	2015;4:1. doi: 10.1186/2046-4053-4-1
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21	15	and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. <i>Bmj</i>
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Table 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

Section and topic	Item N <sub>0</sub>	Checklist items	page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify	Not applicabl
Registration Authors:	2	If registered, provide the name of the registry (such PROSPERO) and registration number	1 1
Contact	3a	Provide name, institutional, e-mail address of all protocol authors, provide physical mailing address of the corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identity the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise state plan for documenting important protocol amendments	Not applicabl
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), if any, in developing the protocol	9
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic databases, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies ( such as two independent reviewers)	6
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	
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Data collection process	11c	through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis) Describe planned method of extracting data from reports (such as piloting forms, done	6
		independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources),	7
		any pre-planned data assumptions and simplifications	
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of main and	5
prioritization		Additional outcomes, with rationale	
Risk of bias in	141	Describe anticipated methods for assessing risk of bias of individual studies, including whether	7
individual studies		this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration	
		of consistency (such as I2, Kendall's $\tau$ )	
	15c	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-	
	150	regression)	
	15d	15d If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies,	8
Confidence in	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8
cumulative evidence			
		selective reporting within studies) Describe how the strength of the body of evidence will be assessed (such as GRADE)	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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# **BMJ Open**

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

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<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Salmonella, Middle East, North Africa, food born disease



### **BMJ Open**

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4 5 6 7	1	Enteric Salmonella in humans and food in the Middle East and North Africa:
	2	Protocol of a systematic review
8 9 10	3	Karima Chaabna <sup>1,2*</sup> and Walid Alali <sup>3</sup>
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### 1 Abstract

### 2 Introduction

3 Nontyphoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. This

- 4 protocol provides methods that will be used to synthesize available epidemiological data on nontyphoidal
- 5 enteric *Salmonella* in humans and food in Middle East and North Africa (MENA) region; and to
- 6 characterize the morbidity of human salmonellosis in this region.

## 7 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 PRISMA 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. 

- 19 Ethics and dissemination
- 20 The results of the systematic review will be disseminated in a peer-reviewed journal and presented at21 relevant conferences.
- 22 Trial registration number
- CRD42016046360
- 24 Keywords
- 25 Enteric Salmonella, Middle East and North Africa

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# **BMJ Open**

1 2		
3 4	1	Strengths and limitations of this study
5 6	2	• To the best of our knowledge, this is the first systematic review evaluating the epidemiology of
7 8	3	nontyphoidal enteric Salmonella in humans and food in the countries of the Middle East and
9 10	4	North Africa region.
11	5	• This systematic review will potentially inform policy makers in order to strengthen national
12 13	6	foodborne disease surveillance and to improve food safety in this region.
14 15	7	• One of our limitations will be probably a high heterogeneity between studies related to sample
16	8	size, populations, settings, study periods, and the use of different biological assays to ascertain the
17 18	9	infection.
19 20	10	size, populations, settings, study periods, and the use of different biological assays to ascertain the infection.
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### 1 Introduction

Nontyphoidal *Salmonella* is considered one of the leading causes of foodborne disease worldwide. The
World Health Organization (WHO) estimated that the annual median number of nontyphoidal
salmonellosis was 78.7 million foodborne illnesses with over 59 thousand deaths <sup>1</sup>. As for the WHO
defined Eastern Mediterranean Region, the median incidence rate of nontyphoidal salmonellosis was
1,610 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<sup>2</sup>.

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 health care system in MENA region differ widely. Although foodborne disease outbreaks have been frequently reported in MENA region, a rigorous reporting and monitoring system (i.e., 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. Nontyphoidal *Salmonella* species are common cause of foodborne disease in the MENA region<sup>1</sup>. 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 that systematically reviewed, synthetized, and assessed the available data on nontyphoidal enteric Salmonella in humans and food in the MENA region. Synthetizing the data in addition to characterizing 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 prioritize food control intervention programs.

## **Objectives**

The proposed systematic review will identify, synthetize, and assess the available data on nontyphoidal
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 nontyphoidal salmonellosis morbidity in human
populations in MENA?, 2) What is the nontyphoidal *Salmonella* prevalence in food in MENA?, 3) What
is the distribution of *Salmonella* serotypes in human populations and food?

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Methods and analysis
 This systematic review protocol was developed based on the Cochrane Collaboration handbook <sup>3</sup> and
 reported following the statement outlined by Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P) 2015 statements <sup>4</sup>. PRIMSA-P 2015 checklist <sup>5</sup> was completed and can
 be found in the Research checklist.
 Inclusion and exclusion criteria

# 7 *Types of studies*

All reports meeting the inclusion criteria will be included if the study sample size is higher than ten. 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.

# 12 *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.

# 16 *Types of exposures*

Included reports are those studying nontyphoidal enteric Salmonella. These reports need to present studies 17 18 that used laboratory testing for Salmonella ascertainment. More precisely, in humans, the laboratory 19 testing have to be conducted on stool samples; i.e., reports of studies based on clinical diagnosis without 20 any laboratory tests on stool to confirm the causative agent will be excluded. Therefore, reports on 21 nontyphoidal 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 22 23 nontyphoidal enteric Salmonella cultured from cerebrospinal fluid will be excluded. Reports referring to 24 nontyphoidal enteric Salmonella infection as Salmonella infection or as salmonellosis will be included; whereas, those referring to enteric Salmonella as typhoidal, paratyphoidal, or invasive nontyphoidal 25 26 Salmonella infection (that is not foodborne or cause of gastro-intestinal tract infections) will be excluded.

# 27 Types of outcomes

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

#### 

## 1 Data sources and search strategy

Our systematic review will be conducted based on the Cochrane Collaboration handbook<sup>3</sup> 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<sup>6</sup>, Embase<sup>7</sup>, CAB Direct<sup>8</sup>, and Global health Library (WHO)<sup>9</sup> databases in order to identify further relevant reports (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/EMR<sup>10</sup> definition of MENA region and we will complement this list with four countries whose official languages are Arabic<sup>11</sup> and that are cited in other definitions of MENA<sup>12-14</sup>. The reviewer team do not speak the official language of Cyprus<sup>11</sup> nor the media of instruction in its Universities and Colleges<sup>15</sup>; this will prevent us to identify grey literature such as reports from the ministry of health, journal articles and conference abstract 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, Svria. Tunisia, United Arab Emirates, and Yemen. The selected MENA countries have a total population of more than 680 million people<sup>16</sup>. 

### 21 Study records

### 22 Selection process

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

## 28 Data collection process

A piloted standardized form developed in Microsoft Excel 2010<sup>18</sup> 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, among others), study characteristics (year of data collection, study site and design, sampling methodology, prevalence, number of positive cases, sample size, among others), biological assay characteristics, individuals' demographic characteristics (age, gender, among others), and on primary and secondary outcomes of interest. **Risk of bias in individual studies** Based on the Cochrane approach<sup>3</sup>, 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. A ROB will be considered low if these three quality domains are probability-based, ascertainment by biological assays, or response rate is $\geq$ 80%, respectively. At outcome-level, a minimum sample size will be calculated using exact binomial confidence interval formula<sup>19</sup> 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 <sup>20</sup> and PRISMA for Abstracts Checklist <sup>21</sup>. We will qualitatively synthesize the identified data on nontyphoidal 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 diarrhea due to gastrointestinal 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.<sup>22</sup> using the meta<sup>23</sup> and metafor<sup>24</sup> packages. Using meta-analysis, we aim to estimate pooled prevalence of Salmonella in food (stratified by category: poultry, beef, and seafood, among others) 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<sup>3</sup> 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.

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2	Meta-bias					
3	Regarding meta-bias assessment, we will use funnel plots in order to explore small-study effect on the					
4	pooled estimates <sup>25</sup> . Traditional funnel plots (log (odds proportion) vs. 1/standard error) are inaccurate for					
5	meta-analysis of proportion studies. Therefore, we will create funnel plots of log (odds proportion)					
6	against sample size $^{26}$ . In order to test the asymmetry of the funnel, we will perform Egger test $^{25}$ that is					
7	based on standard error as well as Peter test which is based on sample size $^{2627}$ .					
8	Confidence in cumulative evidence					
9	We will use a narrative justification for the quality of the evidence at the country-level. We will consider					
10	the quality of evidence being better in a country if at least one country-level study was conducted. This					
11	country-level study should have used standard methodology including probability-based sampling. Thus,					
12	we will categorize countries as having:					
13	- No evidence: no data identified					
14	- Poor evidence: poor quality of the outcome measures					
15	- Limited evidence: the number of outcome measures is small but of reasonable quality					
16	- Good evidence: the number of outcome measures is small but with good quality					
17	- Conclusive evidence: enough outcome measures with good quality					
18	Discussion					
19	To the best of our knowledge, this systematic review will be the first attempt to synthetize available data					
20	on nontyphoidal enteric Salmonella in humans and food in the countries of the MENA region; and to					
21	characterize the morbidity of human salmonellosis. This work will enable us to identify key pathogen					
22	control points that should be reinforced and those that need to be further assessed through country-level					
23	studies. Ultimately, this systematic review will provide rational basis for source attribution studies at both					
24	regional and country levels <sup>28</sup> . Additionally, this study will inform policy maker actions in order to					
25	strengthen national foodborne disease surveillance and to improve food safety and public health in					
26	MENA.					
27	Ethics and dissemination					
28	Ethical approval will not be needed as in this systematic review, data used will not be individual patient					
29	data. Therefore, there will be no concerns about privacy. The findings will be disseminated via					
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30 publication of a manuscript in a peer-reviewed journal and presented at relevant conferences.

#### Author contributions:

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.

#### **Funding statement**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors'. 

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Search criteria - PubMed

("Salmonella" [Mesh] OR "Salmonella" [Text] OR "salmonellosis" [Text])

# AND

("Qatar" [Mesh] OR "Bahrain"[Mesh] OR "Oman" [Mesh] OR "Saudi Arabia" [Mesh] OR "Kuwait" [Mesh] OR "United Arab Emirates" [Mesh] OR "UAE" [Text] OR "U.A.E" [Text] OR "Emirat\*" [Text] OR "Qatar\*" [Text] OR "Oman\*" [Text] OR "Saudi Arabia" [Text] OR "Saudi\*"[Text] OR "Kuwait\*" [Text] OR "United Arab Emirates" [Text] OR "Bahrain\*"[Text] OR "Gulf"[Text] "Yemen"[Mesh] OR "Yemen\*"[Text] OR

"Jordan" [Mesh] OR "Lebanon" [Mesh] OR "Syria" [Mesh] OR "Iraq" [Mesh] OR "Palestine" [Mesh] OR "Jordan" [Text] OR "Lebanon" [Text] OR "Syria" [Text] OR "Iraq" [Text] OR "Palestine" [Text] OR "Jordan\*" [Text] OR "Lebanon" [Text] OR "Lebanese\*" OR "Syria\*" [Text] OR "Iraq\*" [Text] OR "Palestine"] [Text] OR "West Bank" [Text] OR "Gaza" [Text] OR "Palestinian\*" [Text] OR

"Africa,Northern" [Mesh] OR "Algeria" [Mesh] OR "Libya" [Mesh] OR "Egypt" [Mesh] OR "Morocco" [Mesh] OR "Tunisia" [Mesh] or "Mauritania" [Mesh] OR "Algeria" [Text] or "Libya" [Text] OR "Morocco" [Text] OR "Tunisia" [Text] OR "Mauritania" [Text] OR "Egypt" [Text] OR "Algeria\*" [Text] OR "Libya\*" [Text] OR "Moroccan\*" [Text] OR "Tunis\*" [Text] OR "Mauritania\*" [Text] OR "North Africa" [Text] OR "North-Africa" [Text] OR ("Africa" [Text] AND "Northern" [Text]) OR "Northern Africa" [Text] OR "Maghreb" [Text] OR "Maghrib" [Text] OR

"Djibouti"[Mesh] OR "Somalia"[Mesh] OR "Sudan"[Mesh] OR "Africa, Eastern"[Mesh] OR "Djibouti\*"[Text] OR "Somalia\*"[Text] OR "Sudan\*"[Text] OR "East\* Africa\*"[Text] OR

"Afghanistan" [Mesh] OR "Afghan\*" [Text] OR "Pakistan" [Mesh] OR Pakistan\* [text] OR "Iran" [Mesh] OR Iran\* [text] OR "persia" [Mesh] OR Persia\* [text])

Table 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

A J	$N_0$		
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify	Not applicabl
Registration Authors:	2	If registered, provide the name of the registry (such PROSPERO) and registration number	1 1
Contact	3a	Provide name, institutional, e-mail address of all protocol authors, provide physical mailing address of the corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identity the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify	Not
	·	as such and list changes; otherwise state plan for documenting important protocol amendments	applicabl
Support:			
	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), if any, in developing the protocol	9
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic databases, including planned limits, such that it could be repeated	6
Study records:		· 1	
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies ( such as two independent reviewers)	6
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

Data collection process	11c	through each phase of the review ( that is, screening, eligibility, and inclusion in meta-analysis) Describe planned method of extracting data from reports (such as piloting forms, done	6
Data concerton process	110	independently, in duplicate), any processes for obtaining and confirming data from investigators	0
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources),	7
		any pre-planned data assumptions and simplifications	
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of main and	5
prioritization		additional outcomes, with rationale	_
Risk of bias in	141	Describe anticipated methods for assessing risk of bias of individual studies, including whether	7
individual studies		this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
2	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods	
		of handling data and methods of combining data from studies, including any planned exploration	
	15c	of consistency (such as I2, Kendall's $\tau$ ) 15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-	
	150	regression)	
	15d	15d If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies,	8
		selective reporting within studies)	
Confidence in	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8
cumulative evidence			
		selective reporting within studies) Describe how the strength of the body of evidence will be assessed (such as GRADE)	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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