

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Burden of seasonal influenza in sub Saharan Africa: A protocol for systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022949
Article Type:	Protocol
Date Submitted by the Author:	15-Mar-2018
Complete List of Authors:	Sambala, Evanson; South African Medical Research Council, Cochrane ; Malawi Public Health Forum Mdolo, Aaron; University Research Co., LLC (URC) , Centre for Human Services; Malawi Public Health Forum Banda, Richard; University of Cape Town, South Africa , Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health,; Malawi Public Health Forum Phiri, Arthur ; Malawi Public Health Forum Wiyeh, Alison; South African Medical Research Council, Cochrane, South Africa Wiysonge, Charles; Stellenbosch University, Centre for Evidence-Based Health Care; South African Medical Research Council, Cochrane, South Africa
Keywords:	Seasonal influenza, epidemiological burden, influenza-like illnesses (ILI), severe acute respiratory infections (SARI), sub Saharan Africa

SCHOLARONE™
Manuscripts

Only

1
2
3 Burden of seasonal influenza in sub Saharan Africa: A protocol for systematic review and meta-
4 analysis
5

6
7 Authors: Evanson Z Sambala^{1,4}, Aaron Mdolo^{2,4}, Richard Banda^{3,4}, Arthur Phiri⁴, Alison B
8 Wiyeh¹, Charles S Wiysonge^{1,5,6}
9

10
11
12 ¹Cochrane South Africa, South African Medical Research Council, Tygerberg, South Africa
13

14
15 ² University Research Co., LLC (URC) | Centre for Human Services. Malawi Lab Project.
16

17
18 ³ Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health,
19 University of Cape Town, South Africa
20

21
22 ⁴ Malawi Public Health Forum, Malawi
23

24
25 ⁵Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics,
26 Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University,
27 Cape Town, South Africa
28

29
30
31 ⁶School of Public Health and Family Medicine, University of Cape Town, Cape Town, South
32 Africa
33

34
35 **Email addresses of Authors:**
36

37
38 Charles.Wiysonge@mrc.ac.za; Aaron.mdolo@gmail.com; Richardbanda45@gmail.com;
39
40 Arthurmacphiri@gmail.com; Wberiliy@yahoo.co.uk
41

42
43 **Corresponding Author**

44
45 Evanson Z Sambala: Cochrane South Africa, PO Box 19070, Tygerberg 7505, South Africa,
46 Francie van Zijl Drive, Parow Valley, 7505, South Africa
47

48
49 Email: Evanson_sambala@yahoo.com
50
51
52
53
54
55
56
57

Abstract

Introduction: Epidemiological burdens (e.g. clinical attack rates, hospitalization and mortality) are an important contribution to estimating and determining the at risk population due to seasonal influenza. However, in the absence of these burdens, it is extremely difficult for policymakers to decide or prioritize which subpopulation get the limited resources and when. This systematic review will synthesize the literature that have reported the burden of seasonal influenza in Sub Saharan Africa.

Method and analysis: We will include observational studies that capture the epidemiological burden of seasonal influenza. We will perform a multiple electronic database search using Medline, Cinahl, PubMed Central, Embase, African Journal Online (AJOL), Cochrane, Web of science and Google scholar to identify the appropriate titles for studies. We will also perform hand searches of the reference sections of all relevant studies. The identified titles and abstracts will be screened independently by two authors. The full text articles of potentially eligible studies will also be screened independently by two authors. Discrepancies will be resolved by discussions and a third author will be invited to arbitrate if the first two cannot come to a consensus. We will use a Meta command to aggregate estimate measures. The random-effects models and fixed effects models of regression coefficients, odds ratios or hazard ratios will be used for pooled data analysis. Sub-group analyses will be explored if age-standardized mortality, attack and hospitalization rates' and other characteristics of the data are available. We will also assess study quality and risk of bias.

Ethics and communication: We will conduct a systematic review using publicly available data as such no formal ethical review was required. Our findings will be published in a peer review

1
2
3 journal and subsequently disseminated to policymakers through conferences and stakeholder
4
5 meetings.
6

7 **Protocol registration number:** This protocol is registered with the International Prospective
8
9 Register of Systematic Reviews, registration number CRD42017074091
10
11
12
13

14 **Strengths and limitation of this study**

- 15
16
17 • There is a dearth of epidemiological information on seasonal influenza in sub Saharan
18
19 Africa including its impacts thus this study provides an excellent opportunity for
20
21 assessment of the situation in more detail, making the proposed review relevant to inform
22
23 policymakers.
24
- 25
26 • This review assess the epidemiological burdens of seasonal influenza without placing any
27
28 restriction on the language in order to capture all the relevant literature.
29
- 30
31 • We anticipate a wide variation in the identified results as such pooled data will be tested
32
33 for heterogeneity and non-heterogeneity by deliberately dropping one study with the most
34
35 variability one at a time from the analyses.
36
37
- 38
39 • The overall understanding of the burdens of seasonal influenza in sub Saharan Africa will
40
41 provide information for treatment, prevention and control strategies against seasonal
42
43 influenza.
44
45
46
47
48
49
50
51
52
53
54
55
56
57

Introduction

Seasonal influenza is a respiratory illness common among persons with certain chronic diseases, children and the elderly. It is a public health problem, causing severe illness in about 3 to 5 million people and responsible for 290 000 to 650 000 deaths worldwide each year.¹ Seasonal influenza affects individuals of all ages but complications are more common in those younger than 5 years of age or frail adults over 65. The age-specific mortality is highest in individuals over 65 years of age, accounting for 90% of deaths.² Attack rates in susceptible populations, such as school going children or those in nursing homes have been found to be as high as 40-50%.³ Clinical influenza attack rates range from 34% to 67% and rate of hospitalization varies, with children admitted to hospital with Acute Respiratory Infection (ARI), from which influenza virus is identified, varying from 0%-15.6%.⁴

Although seasonal influenza produces lower-level activity in space and time, its cumulative mortality from regular epidemics are greater overall than that of rare pandemics. For instance, cumulative seasonal influenza mortality accrued between 1957 and 1968 exceeded the mortality of the influenza pandemics of 1957 and 1968 in the United States. The influenza pandemics of the 1957 and 1968 caused about 98,000 excess deaths but seasonal influenza deaths were double the excess deaths between 1957 and 1968, excluding the pandemic years.⁵

The effects of seasonal influenza epidemics in Africa are not fully known, but research estimates that 99% of deaths in children under 5 years of age with influenza related lower respiratory tract infections are found in developing countries.⁶ For example, seasonal influenza is an important cause of pneumonia in children and the mortality rates in children due to pneumonia are highest in Africa.⁷ Infection with seasonal Influenza leads to hospitalization with resultant losses in

1
2
3 working days due to sickness, reduction in quality of life due to secondary infections, increased
4 school absenteeism, and increased use of hospital resources.⁸
5
6

7 Seasonal influenza follows predictable seasonal patterns because it is caused by viruses that are
8 already in circulation. In the northern hemisphere, seasonal influenza outbreaks occur between
9 November and March, while in the southern hemisphere seasonal influenza occurs between April
10 and September. Seasonal influenza activity in the tropical region is not strictly seasonal as it
11 occurs throughout the year, with bi-seasonal peaks in summer and winter.^{9 10}
12
13
14
15
16
17
18

19 The purpose of this study is synthesize the literature that have reported the burden of seasonal
20 influenza in sub Saharan Africa.
21
22
23
24
25

26 **Why is it important to do this review?**

27
28 The World Health Organization (WHO) recommends reinforcement of routine epidemiological
29 and virological surveillance in order to ensure timely detection of outbreaks and management of
30 cases.¹¹ In 2002, the WHO pledged to support the Integrated Disease Surveillance Response
31 (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of
32 seasonal influenza. Through surveillance systems, it was anticipated that hospitals and
33 laboratories would document useful data for assessing the burden of seasonal influenza.
34
35 However, there is a dearth of epidemiological information on seasonal influenza including its
36 impacts (mortality, attack rates, susceptibility and hospitalization) in sub Saharan African
37 countries. The aim of this review is to investigate the epidemiological burden of seasonal
38 influenza and highlight its epidemiological patterns in sub Saharan African countries. Our
39 findings will contribute to the better understanding of the burden of seasonal influenza and will
40 be useful in the planning for and response to seasonal influenza outbreaks.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

Type of studies to be included

Observation studies conducted in sub Saharan African countries reporting on the burden of seasonal influenza will be included. Studies that do not report primary data or without explicit description of the methodology will be excluded.

Participants

We will include studies conducted irrespective of age, race or gender in sub Saharan Africa. We will pull and group similar studies together according to the subgroup population. Studies reporting the burden in age clusters not representative of these subpopulation will be excluded. We will also exclude all the population that were affected by the 2009 pandemic influenza. The 2009 pandemic was declared in April, 2009 and by August 2010 the pandemic moved into the post-pandemic period.¹² We will exclude all studies during this period.

Types of outcome measures

In order to be considered for inclusion, studies should explicitly report one or more epidemiological burden estimates. This may refer to mortality rates, attack rates, hospitalization or admission rates, incidence rates or prevalence rates. We will adopt the following definition of the outcome measures. Mortality rate defined as a measure of the number of deaths associated to seasonal influenza. Attack rate will refer to the frequency of morbidity in at risk population while hospitalization rate is a proportion of admissions due to seasonal influenza virus infections. Incidence rate is the number of new cases per population at risk in a given time period whereas

1
2
3 prevalence rate is a measurement of all individuals affected by the disease at a particular times.
4

5 We will exclude economic studies that report burden indicators such as financial costs associated
6
7 to influenza, quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).
8
9

10 11 12 **Data collection** 13

14 We will construct a comprehensive search strategy using key words and MESH terms which will
15
16 be used to search Medline, Cinahl, PubMed Central, Embase, African Journal Online (AJOL),
17
18 Cochrane, Web of science and Google scholar for relevant studies. A computerized search will
19
20 be followed by manual checks of reference sections of all relevant studies. All the identified
21
22 titles and abstracts will be examined and carefully completed by hand. If relevant, a full text
23
24 article would be obtained and read carefully. The titles searched by hand will be retained into the
25
26 database search for a full text. The medical subject heading (MeSH) terms influenza (human) OR
27
28 inter-pandemic influenza, sentinel or virologic surveillance, mortality, morbidity, hospitalization,
29
30 admission rates, clinical attack rates, Influenza Like Illnesses (ILI) (outpatients), Severe Acute
31
32 Respiratory Infections (SARI) and Africa will be used to combine searches systematically. The
33
34 search strategy for Pubmed is shown in table 1.
35
36
37
38

39
40 [Insert Table 1 here- embed at the end of the manuscript]
41
42
43

44 Our search will not place any search limitation on the outcome of the burdens of seasonal
45
46 influenza or date except for the study location. Full text in other languages will be translated into
47
48 English.
49
50

51 52 53 **Data synthesis and sensitivity analysis** 54 55 56 57

1
2
3 A descriptive analysis of the study outcomes will be undertaken. Quantitative estimates will be
4
5 obtained from all eligible studies and pooled for a statistical meta-analysis by use of STATA
6
7 software if we find that studies are similar. We will use a Meta command to aggregate estimate
8
9 measures. The random-effects models and fixed effects models of regression coefficients, odds
10
11 ratios or hazard ratios will be used for pooled data analysis. If necessary, all studies of good
12
13 methodological quality will be combined. Heterogeneity will be tested using the I-squared
14
15 statistic. Heterogeneity and non-heterogeneity will be tested by deliberately dropping one study
16
17 with the most variability one at a time from the analyses. If statistical heterogeneity is present, a
18
19 subgroup analyses will be undertaken to examine the source of the poor data quality. A forest
20
21 plot on all data points and random effects estimates will be generated to give insight to the
22
23 analyses.
24
25
26
27
28
29
30

31 **Risk of bias (quality) assessment**

32
33 Two independent reviewers will retrieve, screen and assess the risk of bias in the identified
34
35 studies. The reviewers will assess the quality of evidence according to the Grading of
36
37 Recommendations Assessment, Development and Evaluation (GRADE) system.¹³ The tool
38
39 encompasses six domains of which each domain include one or more specific entries in the risk
40
41 table describing the study and assigning judgment relating to the risk of bias for that entry.¹³ We
42
43 will judge the risk of bias as either high risk, low risk or unclear risk based on the quality
44
45 evidence for each study. We will develop a risk of bias table to summarize our assessments. Any
46
47 disagreements or discrepancies will be resolved by discussion and if any disagreement cannot be
48
49 resolved an involvement of a third reviewer will be recommended.
50
51
52
53
54
55
56
57
58
59
60

Reporting of this review

We will complete and record the inclusion and exclusion processes using a PRISMA flow chart to capture in detail the reasons for inclusion and exclusion at each stage. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.¹⁴

Ethics and communication

We will conduct the systematic review and meta-analysis using the publicly available data as such no formal ethical review was required. Our findings will be published in a peer review journal and subsequently disseminated to policymakers through conferences and stakeholder meetings.

Patient and public involvement

Patient and public were not involved.

Discussion

There is a lack of epidemiological and laboratory surveillance data on the burden of seasonal influenza in Africa.¹⁵ This lack of information specifically attack rates, susceptibility and hospitalization may undermine the role of seasonal influenza vaccination programme specifically in terms of how it should be implemented. Careful understanding of seasonal influenza, through continuous collection of surveillance and monitoring data of influenza activity taking place at any time of the year, will assist policymakers in preparing for and to strengthening capacity for seasonal influenza surveillance and reporting. The overall understanding of the burden of

1
2
3 seasonal influenza in African settings will subsequently provide information for treatment,
4 prevention and control strategies of seasonal influenza such as giving the vaccines to high risk
5 groups first. We also hope that strengthening surveillance systems for seasonal influenza that
6 report on the burden of viruses will rapidly help detect and send early signals of an impending
7 new influenza activity in humans. It can also be a predictive indicator to aid estimates of
8 additional capacities that may be may needed to deal with a new pandemic activity in an event it
9 occurs.¹⁶
10
11
12
13
14
15
16
17
18
19
20

21 **Authors' contributions**

22 CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS
23 wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and
24 edited the manuscript draft and search strategy. All authors approved the manuscript.
25
26
27
28
29
30
31
32

33 **Funding statement:**

34 This research received no specific grant from any funding agency in the public, commercial or
35 not-for-profit sectors'.
36
37
38
39
40
41

42 **Competing interests statement:**

43 None
44
45
46
47
48

49 **Patient consent:**

50 Not required.
51
52
53
54

55 **References**

- 1
2
3 1. World Health Organization. Influenza (Seasonal) [Internet]; c2018 [cited 2018 February/19].
4 Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/>.
5
- 6
7 2. Rüttimann RW, Bonvehí PE, Vilar-Compte D, Isturiz RE, Labarca JA, Vidal EI. Influenza
8 among the elderly in the americas: A consensus statement. *Revista Panamericana De Salud*
9 *Pública* 2013,33:446-52.
10
- 11 3. Cox N, Subbarao K. Global epidemiology of influenza: Past and present. *Annu Rev Med*
12 2000,51:407-21.
13
- 14 4. Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-saharan africa: A
15 systematic review. *The Lancet Infectious Diseases* 2011,11:223-35.
16
17
- 18 5. Nguyen-Van-Tam JS. Epidemiology of influenza. *Textbook of Influenza* 1998,181-206.
19
- 20 6. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, Simmerman JM, Gordon A,
21 Sato M, Howie S. Global burden of respiratory infections due to seasonal influenza in young
22 children: A systematic review and meta-analysis. *The Lancet* 2011, 378:1917-30.
23
24
- 25 7. Zar HJ, Madhi SA, Aston SJ, Gordon SB. Pneumonia in low and middle income countries:
26 Progress and challenges. *Thorax* 2013, 68:1052-6.
27
- 28 8. Klepser ME. Socioeconomic impact of seasonal (epidemic) influenza and the role of over-the-
29 counter medicines. *Drugs* 2014, 74:1467-79.
30
31
- 32 9. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. *PLoS Medicine* 2006,
33 3(4):e89.
34
- 35 10. Simonsen L, Viboud C, Taylor RJ, Miller MA. The epidemiology of influenza and its
36 control. In: *Influenza vaccines for the future*. Springer; 2011. .
37
38
- 39 11. Steffen C, Debellut F, Gessner B, Kasolo F, Yahaya A, Ayebazibwe N, Bassong O, Cardoso
40 Y, Kebede S, Manoncourt S. Improving influenza surveillance in sub-saharan africa. *Bull*
41 *World Health Organ* 2012, 90:301-5.
42
43
- 44 12. World Health Organization. Pandemic (H1N1) 2009
45 [Internet]; c2018 [cited 2018 February/19]. Available from:
46 <http://www.who.int/csr/disease/swineflu/en/>.
47
- 48 13. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou
49 P, DeBeer H, et al. GRADE guidelines: 1. introduction-GRADE evidence profiles and
50 summary of findings tables. *J Clin Epidemiol* 2011, 64:383-94.
51
52
- 53 14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M,
54 Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic
55
56
57

reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Medicine 2009, 6:e1000100.

15. Katz MA, Schoub BD, Heraud JM, Breiman RF, Njenga MK, Widdowson M. Influenza in Africa: Uncovering the Epidemiology of a Long-Overlooked Disease 2012.
16. World Health Organization. Pandemic Influenza Risk Management WHO Interim Guidance [Internet]; c2013 [cited 2018 February/19]. Available from: http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf.

Table 1: Search Strategy

```

((((("africa"[MeSH Terms] OR "africa"[All Fields]) AND ((((((("epidemiology"[Subheading] OR
"epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) OR
("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR
"prevalence"[MeSH Terms])) OR ("mortality"[Subheading] OR "mortality"[All Fields] OR
"mortality"[MeSH Terms])) OR ("hospitalisation"[All Fields] OR "hospitalization"[MeSH
Terms] OR "hospitalization"[All Fields])) OR ADMISSION[All Fields]) OR ("influenza,
human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human
influenza"[All Fields] OR "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND
ILLNESS[All Fields]))) AND ((((((("influenza, human"[MeSH Terms] OR ("influenza"[All
Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All
Fields]) AND LIKE[All Fields] AND ILLNESS[All Fields]) OR (SEVERE[All Fields] AND
ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All
Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract
infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR
"respiratory infections"[All Fields]))) OR ((("virology"[MeSH Terms] OR "virology"[All
Fields] OR "virologic"[All Fields]) AND ("epidemiology"[Subheading] OR
"epidemiology"[All Fields] OR "surveillance"[All Fields] OR "epidemiology"[MeSH Terms]
OR "surveillance"[All Fields]))) OR ((("laboratories"[MeSH Terms] OR "laboratories"[All
Fields] OR "laboratory"[All Fields]) AND CONFIRMED[All Fields])) OR
(("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR ("out"[All Fields] AND
"patients"[All Fields]) OR "out patients"[All Fields]) AND VISIT[All Fields])) OR ("reverse
transcriptase polymerase chain reaction"[MeSH Terms] OR ("reverse"[All Fields] AND
"transcriptase"[All Fields] AND "polymerase"[All Fields] AND "chain"[All Fields] AND
"reaction"[All Fields]) OR "reverse transcriptase polymerase chain reaction"[All Fields] OR
("rt"[All Fields] AND "pcr"[All Fields]) OR "rt pcr"[All Fields]))) AND ((((((SEASONAL[All
Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND
"human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR
("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR
"human influenza"[All Fields] OR ("human"[All Fields] AND "influenza"[All Fields]))) OR

```

1
2
3
4 (INTER[All Fields] AND ("pandemics"[MeSH Terms] OR "pandemics"[All Fields] OR
5 "pandemic"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields]
6 AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]))
7 OR (("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields])
8 AND CONFIRMED[All Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All
9 Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All
10 Fields])) OR (ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR
11 ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR
12 "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All
13 Fields]) OR "respiratory infections"[All Fields])) OR (("influenza, human"[MeSH Terms] OR
14 ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR
15 "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND ACUTE[All Fields] AND
16 LOWER[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All
17 Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract
18 infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR
19 "respiratory infections"[All Fields]))

BMJ Open

Burden of seasonal influenza in sub Saharan Africa: A systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022949.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Jul-2018
Complete List of Authors:	Sambala, Evanson; South African Medical Research Council, Cochrane ; Malawi Public Health Forum Mdolo, Aaron; University Research Co., LLC (URC) , Centre for Human Services; Malawi Public Health Forum Banda, Richard; University of Cape Town, South Africa , Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health,; Malawi Public Health Forum Phiri, Arthur ; Malawi Public Health Forum Wiyeh, Alison; South African Medical Research Council, Cochrane, South Africa Wiysonge, Charles; Stellenbosch University, Centre for Evidence-Based Health Care; South African Medical Research Council, Cochrane, South Africa
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Seasonal influenza, epidemiological burden, influenza-like illnesses (ILI), severe acute respiratory infections (SARI), sub Saharan Africa

SCHOLARONE™
Manuscripts

Burden of seasonal influenza in sub Saharan Africa: A systematic review protocol

Authors: Evanson Z Sambala^{1,4}, Aaron Mdolo^{2,4}, Richard Banda^{3,4}, Arthur Phiri⁴, Alison B Wiyeh¹, Charles S Wiysonge^{1,5,6}

¹Cochrane South Africa, South African Medical Research Council, Tygerberg, South Africa

² University Research Co., LLC (URC) | Centre for Human Services. Malawi Lab Project, Blantyre, Malawi.

³ Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

⁴ Malawi Public Health Forum, Lilongwe, Malawi

⁵Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

⁶ Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

Email addresses of Authors:

Evanson Z Sambala: Evanson_sambala@yahoo.com; Aaron Mdolo: aaron.mdolo@gmail.com;

Richard Banda: richardbanda45@gmail.com; Arthur Phiri: arthurmacphiri@gmail.com; Alison

B. Wiyeh: wberiliy@yahoo.co.uk; Charles S Wiysonge: Charles.Wiysonge@mrc.ac.za

Corresponding Author

Evanson Z Sambala: Cochrane South Africa, South African Medical Research Council, Francie van Zijl Drive, Parow Valley, PO Box 19070, Tygerberg 7505, South Africa

Abstract

Introduction: Measures of epidemiological burdens are an important contribution to estimating disease severity and determining the at-risk populations for seasonal influenza. In the absence of these data, it is extremely difficult for policymakers to decide on how to distribute limited resources. This systematic review will synthesize the literature on reported burden of seasonal influenza (e.g. morbidity and mortality) in sub Saharan Africa.

Method and analysis: We will include published epidemiological studies that capture the burden estimation of seasonal influenza between January 1, 2000 and April 31, 2018. Studies that have reported disease burden estimates associated to influenza-like illness (ILI), acute respiratory illness (ARI), acute lower respiratory illness (ALRI), severe respiratory illness (SARI), and severe or very severe pneumonia using laboratory confirmed influenza cases will be included. We will perform a multiple electronic database search in PubMed, Embase, African Journal Online (AJOL), Cochrane, Web of science, Cinahl, and Google scholar for eligible studies. The reference lists of relevant studies will also be hand searched for potentially eligible studies. The titles and abstracts of identified records will be screened independently by two authors. The full text articles of potentially eligible studies will be assessed independently by two authors. Discrepancies will be resolved by discussion, and by a third author if the first two authors fail to come to a consensus. The measures of the burden of influenza will be aggregated using a meta-analysis for homogenous studies and narrative synthesis if the studies are heterogeneous. The strength of the evidence will be assessed using the GRADE approach.

Ethics and dissemination: This systematic review will use publicly available data; and as such, no formal ethical review is required. Our findings will be published in a peer-reviewed journal and also disseminated through conferences and stakeholder meetings.

1
2
3 **PROSPERO registration number: CRD42017074091**
4
5
6
7

8 **Strengths and limitation of this study**
9

- 10
- 11 • Due to the variability in the definition and diagnosis of influenza across settings and over
12 time, there may be important differences in the case definitions (error in coding cases),
13 diagnostic sampling and diagnostic assays from various studies. This may lead to
14 overestimation of the disease burden.
15
16
 - 17 • The studies that will be included in this review are observational studies which are more
18 prone to reporting biases and may overestimate the burden of the disease
19
20
 - 21 • The search for relevant studies will include both published and unpublished literature
22 hence minimizing the risk for publication bias.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57

Introduction

Seasonal influenza is a respiratory transmittable infection caused by different subtypes (types A, B, C and D) of influenza viruses. It is a public health problem, causing severe illness in about 3 to 5 million people and responsible for 290 000 to 650 000 deaths worldwide each year.¹ It further remains an important source of economic loss worldwide. The total economic loss in the US due to the burden of influenza amounts to \$87.1 billion every year.² Hospitalization due to seasonal influenza leads to losses in working days due to sickness, reduction in quality of life due to secondary infections, increased school absenteeism, and increased use of hospital resources.³

This condition affects individuals of all ages but complications are more common in those younger than 5 years of age, frail adults over 65, pregnant women and persons with chronic medical conditions. The age-specific mortality is highest in individuals over 65 years of age, accounting for 90% of deaths.⁴ Attack rates in susceptible populations, such as school going children or those in nursing homes have been found to be as high as 40-50%.⁵ Clinical influenza attack rates range from 34% to 67% and rate of hospitalization varies, with children admitted to hospital with Acute Lower Respiratory Infection (ALRI), from which influenza virus is identified, varying from 0%-15.6%.⁶ Severe ALRI would generally include pneumonia but also most commonly present itself as bronchiolitis in children. Mortality rates in children due to pneumonia are highest in Africa.⁷ The research on the global burden of pediatric influenza indicate that 99% of deaths in children under 5 years of age are due to lower respiratory tract infections.⁸

Although seasonal influenza produces lower-level activity in space and time, its cumulative mortality from regular epidemics are greater overall than that of rare pandemics. For instance,

1
2
3 cumulative seasonal influenza mortality accrued between 1957 and 1968 exceeded the mortality
4 of the influenza pandemics of 1957 and 1968 in the United States. The influenza pandemics of
5 the 1957 and 1968 caused about 98,000 excess deaths but seasonal influenza deaths were double
6 the excess deaths between 1957 and 1968, excluding the pandemic years.⁹
7
8
9

10
11 Although much is known about the effects of seasonal influenza, including global estimates of
12 burden of influenza, the majority of studies are derived from developed countries. The burden of
13 seasonal influenza in Africa is not fully known. The purpose of this study is to synthesize the
14 existing studies that have reported the burden of seasonal influenza in sub Saharan Africa.
15
16
17
18
19
20
21
22
23

24 **Why is it important to do this review?**

25
26 The World Health Organization (WHO) recommends reinforcement of routine epidemiological
27 and virological surveillance in order to ensure timely detection of outbreaks and management of
28 cases.¹⁰ In 2002, the WHO pledged to support the Integrated Disease Surveillance Response
29 (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of
30 seasonal influenza. Through surveillance systems, it is anticipated that hospitals and laboratories
31 would document useful data for assessing the burden of seasonal influenza. However, there is a
32 dearth of epidemiological information on seasonal influenza including its impacts (mortality,
33 attack rates, susceptibility and hospitalization) in sub Saharan African countries. The aim of this
34 review is to investigate the epidemiological burden of seasonal influenza and highlight its
35 epidemiological patterns in sub Saharan African countries. Our findings will contribute to the
36 better understanding of the burden of seasonal influenza and will be useful in the planning for
37 and response to seasonal influenza outbreaks in terms of prevention and treatment.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

Eligibility criteria

Type of studies to be included

Epidemiological studies conducted in sub-Saharan African countries and published between January 1, 2000 and April 31, 2018 reporting on the burden of seasonal influenza will be included. These dates coincides with the existence of the integrated disease surveillance response system in Africa. We will include published estimates from studies deriving their data from sentinel surveillance systems or healthcare facilities in which human influenza infection has been verified using a valid laboratory test such as a reverse transcriptase polymerase chain reaction (RT-PCR). Since influenza transmission occur throughout the tropical and sub-tropical areas in Africa, we will consider studies with data reported weekly or monthly for at least a year. The peak periods in influenza in the tropics are between March and September but tend to vary from year to year depending on the type and sub-type of human influenza in circulation.¹¹⁻¹² Studies that estimate the disease burden using modelling techniques will be excluded.

Participants

We will include studies that stratify influenza rates in the following age groups; 0 to <2 years, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years and over 65 years. Where studies are unable to report age stratified estimates within the proposed age groups, we will report rates as suggested in the studies. We will pull and group similar studies together according to the subgroup population based on the WHO case definition of influenza. The WHO case definitions varies across age groups and across study sites. All age specific data for inclusion will be well-defined in terms of numerators (case count) and denominators (population at risk). We will

1
2
3 exclude all studies that use data reported between 31 January 2009 and 1 November 2010
4 including all studies where study duration overlaps or combines the pandemic and non
5 pandemic- periods. The 2009 pandemic influenza was declared in April, 2009 and by August
6
7
8
9
10 2010 it was declared over.¹³ This is based on the assumption that the pandemic virus (H1N1) was
11
12 actively circulating for 6-8 weeks before and after the pandemic period.
13
14
15

16 17 **Types of outcome measures**

18
19 In order to be considered for inclusion, studies should explicitly report one or more
20
21 epidemiological burden estimates. Burden estimates refer to mortality rates, attack rates,
22
23 hospitalization or admission rates, incidence rates or period prevalence rates associated with
24
25 influenza-like illness (ILI) and severe respiratory illness (SARI). We will also adopt the
26
27 following definition of the outcome measures. Mortality rate is defined as a measure of the
28
29 number of deaths in a specific age group due to seasonal influenza divided by population of age
30
31 group expressed in 1,000 person years. Attack rate refers to number of new cases of disease
32
33 during specified time interval divided by the number of persons or age groups at risk in the
34
35 population at the start of a time interval. Hospitalization rate is the number of influenza inpatient
36
37 admissions discharged over a specific time and geographical area divided by the population in
38
39 that age group, expressed in terms of 1000 people days. Incidence rate is the number of new
40
41 cases per population at risk in a given time period whereas period prevalence rate is a
42
43 measurement of new and preexisting of all individuals affected by the disease over a specified
44
45 period of time divided by total number of people in that population. As far as prevalence
46
47 estimates are concerned we will only focus on period prevalence.
48
49
50
51
52
53
54
55
56
57
58
59
60

Case definitions of influenza-like illness and severe respiratory illness

We will adopt the WHO case definitions for ILI and SARI used between 1999 and 2018. The 1999 WHO case definition of ILI was defined as “a sudden onset of fever, a temperature $>38^{\circ}$ C and a cough or sore throat in the absence of another diagnosis”.¹⁴ In 2018, ILI was defined as “an acute respiratory illness with measured temperature of $\geq 38^{\circ}$ C and cough, with onset within 10 days”.¹⁵ In 1999, SARI definition did not exist but in 2009 it was officially defined as “a sudden onset of fever $> 38^{\circ}$ C, cough or sore throat, shortness of breath or difficulty breathing, and requiring hospitalization. For those less than 5 years of age, pneumonia was used as criteria including cough or difficulty breathing.”¹⁶ The 2018 definition of SARI (including acute respiratory illness (ARI), acute lower respiratory illness (ALRI) and severe or very severe pneumonia) was “an acute respiratory illness with a history of fever or measured fever of $\geq 38^{\circ}$ C and cough, with onset within the past 10 days, requiring hospitalization.”¹⁵ We will pull studies that report laboratory confirmed influenza in patients with pneumonia that matches the International Classification of Disease codes (ICD-9 codes; 488.01, 488.11 and ICD-10 codes; J09.01, J09.11, J10.0) severe illness. The WHO case definitions for ILI and SARI have changed many times, in 2011, 2014 and 2018 in order to facility valid comparison of disease occurrence over a period of time, and increase the sensitivity and specificity in reporting.

Search method for identification of studies

We will construct a comprehensive search strategy using key words and MESH terms in PubMed, Embase, African Journal Online (AJOL), Cochrane, Web of science, Cinahl, and Google scholar for relevant studies. We will conduct a database search followed by hand searching of reference sections of all relevant studies. The medical subject heading (MeSH)

1
2
3 terms influenza (human) OR inter-pandemic influenza, sentinel or virologic surveillance,
4 mortality, morbidity, hospitalization, admission rates, clinical attack rates, Influenza Like
5
6 Illnesses (ILI) (outpatients), Severe Acute Respiratory Infections (SARI), Acute Lower
7
8 Respiratory Infections (ALRI) and Africa will be used to combine searches systematically. The
9
10 search strategy for PubMed is shown in table 1 but we plan to modify and run slightly different
11
12 search strategy across the different databases. We will not place any restriction on language but
13
14 will limit our search to studies in sub Saharan Africa.
15
16
17
18
19
20

21 **Selection of studies**

22
23 All the identified titles and abstracts will be examined independently for potential eligibility by
24
25 two authors (EZS and AM). Discrepancies will be resolved by consensus and if necessary by
26
27 arbitration by a third author (CSW). The full texts of potentially eligible studies will be retrieved,
28
29 and screened independently by two authors (EZS and AM). Disagreements between the first two
30
31 authors will again be resolved by discussion and consensus and by arbitration by a third author
32
33 (CSW) if necessary.
34
35
36
37
38
39

40 [Insert Table 1 here- embedded at the end of the manuscript]
41
42
43

44 **Data extraction and management**

45
46 Two study authors (EZS and AM) will extract data independently from eligible studies using a
47
48 pre-structured and tested data collection form. The information collected using this form will
49
50 include details on the year the study was conducted, setting, study design, methods, participants
51
52 and outcomes, source of funding and risk of bias. The two authors will compare the extracted
53
54
55
56
57

1
2
3 data and discrepancies will be resolved by consensus or by a third author (CSW) if relevant. In
4
5 the event where there is missing data from included studies which we deem important, we will
6
7 contact the authors of the studies involved.
8
9

12 **Risk of bias (quality) assessment**

14 Two independent reviewers will retrieve, screen and assess the risk of bias in the identified
15
16 studies. In context of surveillance, biases are often present at the sampling stage of
17
18 SARI/ALR/ILI case counts of which many eligible cases are excluded resulting in selection bias.
19
20 In addition, diagnostic assays used to identify cases may lead to misclassification bias. For
21
22 example, RT-PCR identifies more cases than immunofluorescence assays. The risk of bias in
23
24 prevalence studies will be assessed using the risk of bias in prevalence studies in Hoy *et al.*¹⁷
25
26
27
28
29

31 **Data and sensitivity analysis**

32
33 A descriptive analysis of the study outcomes will be undertaken if studies are not eligible to be
34
35 pooled for burden estimates. This will include studies with burden estimates that are not
36
37 representative of the catchment population. Eligible studies will be stratified by type of
38
39 population (i.e. community or hospital setting etc), surveillance type (i.e. active or passive
40
41 surveillance) and type of influenza case definitions (including whether it is based on 1999, 2014
42
43 or 2018 case definition) in order to compare similar designs. We will also stratify the burden
44
45 estimates for ILI and SARI by age or risk group. In an event there are multiple reporting in a
46
47 study we will combine all the studies or use the study with most complete dataset.
48
49

50
51 Quantitative estimates i.e. annual incidence, period prevalence and mortality of influenza, and
52
53 95% CIs will be obtained from all eligible studies and pooled for a statistical meta-analysis by
54
55
56
57

1
2
3 use of STATA software if we find that studies are similar. If burden estimates are reported by
4 week or month, we will calculate yearly burden estimates based on methods provided in the
5 WHO manual for estimating disease burden associated with seasonal influenza.¹⁸ Where studies
6 provide relevant data for the catchment population, we will pool burden proportions of all cases
7 sampled among SARI cases from whom clinical specimen were tested by week/month/year by
8 dividing the total number of SARI cases by month/week/year and multiplying it by 100%. We
9 will adjust for true total number of influenza-associated SARI cases per week/month/year by
10 scaling up the number of influenza positive SARI cases by the proportion of SARI cases tested.
11 To estimate the proportion of ILI cases attributable to laboratory-confirmed influenza illness
12 without population denominators require data on case counts (i.e. number of ILI cases positive
13 for influenza virus using laboratory tests) divided by number of ILI cases from whom clinical
14 specimens were collected for diagnostic testing multiplied by 100. To estimated number of
15 influenza-associated ILI, we will adjust the proportion influenza-associated ILI by week, month
16 or year multiplied by total number of ILI cases by week, month or year. Step by step formulas
17 are presented in in the WHO manual for estimating disease burden associated with seasonal
18 influenza.¹⁸

19 We will use a meta-analysis to aggregate estimate measures. The random-effects models and
20 fixed effects models of regression coefficients will be used for pooled data analysis. If necessary,
21 all studies of good methodological quality will be combined. We anticipate heterogeneity in the
22 pooled studies due to different case definitions for SARI/ILI and origin of data (active and
23 passive surveillance) thus heterogeneity will be tested using the Chi-square test and I-square test
24 statistic. We will consider a significance level of $\alpha = 0.1$ for Chi-square test and I-squared
25 statistic of >50% to reflect significant heterogeneity. Heterogeneity and non-heterogeneity will
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 be tested by deliberately dropping studies with high risk of bias from the analyses one at a time.
4
5 If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the
6
7 source of the poor data quality. We will include case definitions of influenza, passive or active
8
9 studies, representation of the catchment area, age, gender, seasonality (tropical or subtropical),
10
11 duration and type of study as covariates in the Meta analysis. Where there is significant
12
13 heterogeneity, meta-analysis will not be performed. Only studies with similar risk of bias
14
15 assessment will be pooled in a meta-analysis. We will define country burden disease estimates
16
17 yielded from passive sentinel surveillance data (e.g. ILI) as a lower threshold and upper
18
19 threshold for active sentinel surveillance data (e.g. SARI). Passive sentinel surveillance
20
21 substantially yields lower estimates compared to active surveillance data. A forest plot on all
22
23 data points and random effects estimates will be generated to give insight to the analyses. The
24
25 reviewers will assess the strength of the evidence according to the Grading of Recommendations
26
27 Assessment, Development and Evaluation (GRADE) approach.¹⁹ This approach rates the
28
29 strength of the evidence by taking into account five factors: methodological quality, directness of
30
31 evidence, heterogeneity, precision and risk of publication bias.
32
33
34
35
36
37
38
39

40 **Reporting of this review**

41
42 We wrote this protocol following the Preferred Reporting Items for Systematic Review and
43
44 Meta-Analysis Protocols guidelines. PRISMA focuses on ways in which authors can ensure the
45
46 transparent and complete reporting of systematic reviews and meta-analyses.²⁰ The findings of
47
48 this review and any amendments will be reported according to the Preferred Reporting Items for
49
50 Systematic Reviews and Meta-Analyses statement
51
52
53
54
55
56
57
58
59
60

Ethics and communication

We will conduct the systematic review and meta-analysis using the publicly available data as such no formal ethical review was required. Our findings will be published in a peer review journal and subsequently disseminated to policymakers through conferences and stakeholder meetings.

Patient and public involvement

Patient and public were not involved.

Data sharing statement

Additional information beyond that contained within this manuscript can be obtained from the corresponding author.

Discussion and study limitation

There is a lack of epidemiological and laboratory surveillance data on the burden of seasonal influenza in Africa.²¹ This lack of information specifically attack rates, susceptibility and hospitalization may undermine the role of seasonal influenza vaccination programme specifically in terms of how it should be implemented. Careful understanding of seasonal influenza, through continuous collection of surveillance and monitoring data of influenza activity taking place at any time of the year, will assist policymakers in preparing for and to strengthening capacity for seasonal influenza surveillance and reporting. The overall understanding of the burden of seasonal influenza in African settings will subsequently provide information for treatment, prevention and control strategies of seasonal influenza such as giving the vaccines to high risk

1
2
3 groups first. We also hope that strengthening surveillance systems for seasonal influenza that
4 report on the burden of viruses will rapidly help detect and send early signals of an impending
5 new or severe influenza activity in humans. Seasonal influenza burden estimates that provide
6 baseline data can provide valuable information with which to compare annual influenza
7 outbreaks with unusual outbreak events.¹⁸ This information can serve as a predictive indicator for
8 new events such as an influenza pandemic and systematically aid pandemic planners to plan for
9 additional capacities and resources (stockpile of antivirals and antibiotics etc) needed to deal
10 with a severity of a new pandemic activity.²²

21 We anticipate several limitation in our study related to bias in influenza reporting and estimating
22 burden of the disease. Firstly, pooled data from studies will be limited to respiratory infections
23 such as ILI and SARI. As such there is possibility of underestimating influenza related burden
24 caused by other clinical manifestation such as myocardial event triggered by influenza infection.
25 Secondly, ILI surveillance data do not have a known population denominators and many people
26 in the communities or catchment areas may not report influenza associated disease thus making it
27 difficult to extrapolate, for example, incidence rates. Assuming enough information is provided
28 in the studies we will adjust the estimates by using the methodology provided in a similar study²³
29 to ours. Thirdly, while we will take precautions to review studies for quality and relevance, often
30 bias resulting from case definitions (error in coding cases), diagnostic sampling and diagnostic
31 assays are inevitable in eligible studies thus difficult to determine precisely the disease burden
32 estimations once we pool data for analyses. We deliberately intend to use different WHO case
33 definitions of SARI and ILI. However, the implications of this is that much older version of case
34 definition are highly sensitive to children under age of 5 and less sensitive to older children and
35 adults. Further implications of the use of different case definitions is that pooled estimates may
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 not be a reflection of true influenza burden in the population. We intend to reconcile the different
4 case definitions (e.g. SARI cases) in different studies by matching them to hospitalized severe
5 ALRI and pneumonia and influenza (i.e. ICD-9 and ICD-10) making sure there are comparable
6
7
8
9
10 between themselves and help in harmonization and interpretation of data.
11
12
13

14 **Authors' contributions**

15
16 CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS
17 wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and
18
19 edited the manuscript draft and search strategy. All authors approved the manuscript.
20
21
22
23
24
25

26 **Funding statement:**

27
28 This research received no specific grant from any funding agency in the public, commercial or
29 not-for-profit sectors.
30
31
32
33
34

35 **Competing interests statement:**

36
37 None
38
39
40
41

42 **Patient consent:**

43
44 Not required.
45
46
47
48
49

50 **References**

51
52
53 1. World Health Organization. Influenza (Seasonal) [Internet]; c2018 [cited 2018 February/19].
54 Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/>
55
56
57

- 1
2
3 2. Molinari NM, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal
4 influenza in the US: measuring disease burden and costs, *Vaccine* 2007;**25**:5086-96.
5
- 6
7 3. Klepser ME. Socioeconomic impact of seasonal (epidemic) influenza and the role of over-the-
8 counter medicines, *Drugs* 2014;**74**:1467-79.
9
- 10
11 4. Rüttimann RW, Bonvehí PE, Vilar-Compte D, et al. Influenza among the elderly in the
12 Americas: a consensus statement, *Revista Panamericana de Salud Pública* 2013;**33**:446-52.
13
- 14
15 5. Cox N, Subbarao K. Global epidemiology of influenza: past and present, *Annu Rev Med*
16 2000;**51**:407-21.
17
- 18
19 6. Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-Saharan Africa: a
20 systematic review, *The Lancet infectious diseases* 2011;**11**:223-35.
21
- 22
23 7. Zar HJ, Madhi SA, Aston SJ, et al. Pneumonia in low and middle income countries: progress
24 and challenges, *Thorax* 2013;**68**:1052-6.
25
- 26
27 8. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal
28 influenza in young children: a systematic review and meta-analysis, *The Lancet* 2011;**378**:1917-
29 30.
30
- 31
32 9. Nguyen-Van-Tam JS. Epidemiology of influenza, *Textbook of influenza* 1998:181-206.
33
- 34
35 10 Steffen C, Debellut F, Gessner B, et al. Improving influenza surveillance in sub-Saharan
36 Africa, *Bull World Health Organ* 2012;**90**:301-5.
37
- 38
39 11. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions, *PLoS medicine*
40 2006;**3**:e89.
41
- 42
43 12. Simonsen L, Viboud C, Taylor RJ, et al. The epidemiology of influenza and its control. In:
44 Anonymous . Influenza vaccines for the future: Springer 2011:27-54.
45
- 46
47 13. World Health Organisation. Pandemic (H1N1) 2009
48 [Internet]; c2018 [cited 2018 February/19]. Available from:
49 <http://www.who.int/csr/disease/swineflu/en/>.
50
- 51
52 14. World Health Organization. WHO recommended surveillance standards, 1999 [Internet];
53 c1999 [cited 2018 February/19]. Available from:
54 [http://apps.who.int/iris/bitstream/handle/10665/65517/WHO_CDS_CSR_ISR_99.2.pdf?sequenc](http://apps.who.int/iris/bitstream/handle/10665/65517/WHO_CDS_CSR_ISR_99.2.pdf?sequence=1&isAllowed=y)
55 [e=1&isAllowed=y](http://apps.who.int/iris/bitstream/handle/10665/65517/WHO_CDS_CSR_ISR_99.2.pdf?sequence=1&isAllowed=y)
56
- 57
58 15. Fitzner J, Qasmieh S, Mounts AW, et al. Revision of clinical case definitions: influenza-like
59 illness and severe acute respiratory infection, *Bull World Health Organ* 2018;**96**:122.
60

- 1
2
3 16. Ortiz JR, Sotomayor V, Uez OC, *et al.* Strategy to enhance influenza surveillance worldwide,
4 *Emerg Infect Dis* 2009;**15**:1271-8.
5
6
7 17. Hoy D, Brooks P, Woolf A, *et al.* Assessing risk of bias in prevalence studies: modification
8 of an existing tool and evidence of interrater agreement, *J Clin Epidemiol* 2012;**65**:934-9.
9
10 18. World Health Organization. A manual for estimating disease burden associated with seasonal
11 influenza: World Health Organization 2015 [Internet]; c2018 [cited 2018 February/19].
12 Available from:
13 http://apps.who.int/iris/bitstream/handle/10665/178801/9789241549301_eng.pdf?sequence=1
14
15
16 19. Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence
17 profiles and summary of findings tables, *J Clin Epidemiol* 2011;**64**:383-94.
18
19 20. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic
20 reviews and meta-analyses of studies that evaluate health care interventions: explanation and
21 elaboration, *PLoS medicine* 2009;**6**:e1000100.
22
23
24 21. Katz MA, Schoub BD, Heraud JM, *et al.* Influenza in Africa: uncovering the epidemiology
25 of a long-overlooked disease, *J. Infect. Dis* 2012; **206**: S1–S4 21.
26
27 22. World Health Organization. Pandemic Influenza Risk Management WHO Interim
28 Guidance [Internet]; c2013 [cited 2018 February/19]. Available from:
29 [http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementI](http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf)
30 [nterimGuidance_Jun2013.pdf](http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf).
31
32
33 23. Emukule GO, Paget J, van der Velden K, *et al.* Influenza-associated disease burden in
34 Kenya: a systematic review of literature, *PloS one* 2015;**10**:e0138708.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1: Search Strategy

For peer review only

1
 2
 3
 4
 5
 6
 7
 8
 9
 10
 11
 12
 13
 14
 15
 16
 17
 18
 19
 20
 21
 22
 23
 24
 25
 26
 27
 28
 29
 30
 31
 32
 33
 34
 35
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

(((("africa"[MeSH Terms] OR "africa"[All Fields]) AND ((((((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])) OR ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) OR ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields])) OR ADMISSION[All Fields]) OR (("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND ILLNESS[All Fields])) AND ((((((("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND LIKE[All Fields] AND ILLNESS[All Fields]) OR (SEVERE[All Fields] AND ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields])) OR (("virology"[MeSH Terms] OR "virology"[All Fields] OR "virologic"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "surveillance"[All Fields] OR "epidemiology"[MeSH Terms] OR "surveillance"[All Fields])) OR (("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields]) AND CONFIRMED[All Fields])) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR ("out"[All Fields] AND "patients"[All Fields]) OR "out patients"[All Fields]) AND VISIT[All Fields])) OR ("reverse transcriptase polymerase chain reaction"[MeSH Terms] OR ("reverse"[All Fields] AND "transcriptase"[All Fields] AND "polymerase"[All Fields] AND "chain"[All Fields] AND "reaction"[All Fields]) OR "reverse transcriptase polymerase chain reaction"[All Fields] OR ("rt"[All Fields] AND "pcr"[All Fields]) OR "rt pcr"[All Fields])) AND ((((((SEASONAL[All Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR ("human"[All Fields] AND "influenza"[All Fields])) OR (INTER[All Fields] AND ("pandemics"[MeSH Terms] OR "pandemics"[All Fields] OR "pandemic"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR (("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields]) AND CONFIRMED[All Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR (ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields])) OR (("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND ACUTE[All Fields] AND LOWER[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields]))))

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

Burden of seasonal influenza in sub Saharan Africa: A systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022949.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Aug-2018
Complete List of Authors:	Sambala, Evanson; South African Medical Research Council, Cochrane ; Malawi Public Health Forum Mdolo, Aaron; University Research Co., LLC (URC) , Centre for Human Services; Malawi Public Health Forum Banda, Richard; University of Cape Town, South Africa , Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health,; Malawi Public Health Forum Phiri, Arthur ; Malawi Public Health Forum Wiyeh, Alison; South African Medical Research Council, Cochrane, South Africa Wiysonge, Charles; Stellenbosch University, Centre for Evidence-Based Health Care; South African Medical Research Council, Cochrane, South Africa
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	Seasonal influenza, epidemiological burden, influenza-like illnesses (ILI), severe acute respiratory infections (SARI), sub Saharan Africa

SCHOLARONE™
Manuscripts

Burden of seasonal influenza in sub Saharan Africa: A systematic review protocol

Authors: Evanson Z Sambala^{1,4}, Aaron Mdolo^{2,4}, Richard Banda^{3,4}, Arthur Phiri⁴, Alison B Wiyeh¹, Charles S Wiysonge^{1,5,6}

¹Cochrane South Africa, South African Medical Research Council, Tygerberg, Cape Town, South Africa.

² University Research Co., LLC (URC) | Centre for Human Services. Malawi Lab Project, Blantyre, Malawi.

³ Alan J Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa .

⁴ Malawi Public Health Forum, Lilongwe, Malawi.

⁵Centre for Evidence-Based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

⁶ Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

Email addresses of Authors:

Evanson Z Sambala: Evanson_sambala@yahoo.com; Aaron Mdolo: aaron.mdolo@gmail.com;

Richard Banda: richardbanda45@gmail.com; Arthur Phiri: arthurmacphiri@gmail.com; Alison

B. Wiyeh: wberiliy@yahoo.co.uk; Charles S Wiysonge: Charles.Wiysonge@mrc.ac.za

Corresponding Author

Evanson Z Sambala: Cochrane South Africa, South African Medical Research Council, Francie van Zijl Drive, Parow Valley, PO Box 19070, Tygerberg, Cape Town, 7505, South Africa

Abstract

Introduction: Measures of epidemiological burdens are an important contribution to estimating disease severity and determining the at-risk populations for seasonal influenza. In the absence of these data, it is extremely difficult for policymakers to decide on how to distribute limited resources. This systematic review will synthesize the literature on reported burden of seasonal influenza (e.g. morbidity and mortality) in sub Saharan Africa.

Method and analysis: We will include published epidemiological studies that capture the burden estimation of seasonal influenza between January 1, 2000 and August 31, 2018. Studies that have reported disease burden estimates associated to influenza-like illness (ILI), acute respiratory illness (ARI), acute lower respiratory illness (ALRI), severe respiratory illness (SARI), and severe or very severe pneumonia using laboratory confirmed influenza cases will be included. We will perform a multiple electronic database search in PubMed, Embase, African Journal Online (AJOL), Cochrane, Web of science, Cinahl, and Google scholar for eligible studies. The reference lists of relevant studies will also be hand searched for potentially eligible studies. The titles and abstracts of identified records will be screened independently by two authors. The full text articles of potentially eligible studies will be assessed independently by two authors. Discrepancies will be resolved by discussion, and by a third author if the first two authors fail to come to a consensus. The measures of the burden of influenza will be aggregated using a meta-analysis for homogenous studies and narrative synthesis if the studies are heterogeneous. The strength of the evidence will be assessed using the GRADE approach.

Ethics and dissemination: This systematic review will use publicly available data; and as such, no formal ethical review is required. Our findings will be published in a peer-reviewed journal and also disseminated through conferences and stakeholder meetings.

PROSPERO registration number: CRD42017074091

Strengths and limitation of this study

- This systematic review assess the epidemiological burdens of seasonal influenza without placing any restriction on language.
- The search for relevant studies will include both published and unpublished to minimize the risk for publication bias.
- The strength of the evidence in this review will be assessed using the GRADE approach.
- A wide variation in the case definition and diagnostic of influenza may lead to inaccurate estimates of the disease burden.
- The studies that will be included in this review are observational studies which are more prone to reporting biases and may overestimate the burden of the disease.

Introduction

Seasonal influenza is a respiratory transmittable infection caused by different subtypes (types A, B, C and D) of influenza viruses. It is a public health problem, causing severe illness in about 3 to 5 million people and responsible for 290 000 to 650 000 deaths worldwide each year.¹ It further remains an important source of economic loss worldwide. The total economic loss in the US due to the burden of influenza amounts to \$87.1 billion every year.² Hospitalization due to seasonal influenza leads to losses in working days due to sickness, reduction in quality of life

1
2
3 due to secondary infections, increased school absenteeism, and increased use of hospital
4 resources.³
5
6

7 This condition affects individuals of all ages but complications are more common in those
8 younger than 5 years of age, frail adults over 65, pregnant women and persons with chronic
9 medical conditions. The age-specific mortality is highest in individuals over 65 years of age,
10 accounting for 90% of deaths.⁴ Attack rates in susceptible populations, such as school going
11 children or those in nursing homes have been found to be as high as 40-50%.⁵ Clinical influenza
12 attack rates range from 34% to 67% and rate of hospitalization varies, with children admitted to
13 hospital with Acute Lower Respiratory Infection (ALRI), from which influenza virus is
14 identified, varying from 0%-15.6%.⁶ Severe ALRI would generally include pneumonia but also
15 most commonly present itself as bronchiolitis in children. Mortality rates in children due to
16 pneumonia are highest in Africa.⁷ The research on the global burden of pediatric influenza
17 indicate that 99% of deaths in children under 5 years of age are due to lower respiratory tract
18 infections.⁸
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

35 Although seasonal influenza produces lower-level activity in space and time, its cumulative
36 mortality from regular epidemics are greater overall than that of rare pandemics. For instance,
37 cumulative seasonal influenza mortality accrued between 1957 and 1968 exceeded the mortality
38 of the influenza pandemics of 1957 and 1968 in the United States. The influenza pandemics of
39 the 1957 and 1968 caused about 98,000 excess deaths but seasonal influenza deaths were double
40 the excess deaths between 1957 and 1968, excluding the pandemic years.⁹
41
42
43
44
45
46
47
48

49 Although much is known about the effects of seasonal influenza, including global estimates of
50 burden of influenza, the majority of studies are derived from developed countries. The burden of
51
52
53
54
55
56
57
58
59
60

1
2
3 seasonal influenza in Africa is not fully known. The purpose of this study is to synthesize the
4 existing studies that have reported the burden of seasonal influenza in sub Saharan Africa.
5
6
7
8
9

10 **Why is it important to do this review?**

11
12 The World Health Organization (WHO) recommends reinforcement of routine epidemiological
13 and virological surveillance in order to ensure timely detection of outbreaks and management of
14 cases.¹⁰ In 2002, the WHO pledged to support the Integrated Disease Surveillance Response
15 (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of
16 seasonal influenza. Through surveillance systems, it is anticipated that hospitals and laboratories
17 would document useful data for assessing the burden of seasonal influenza. However, there is a
18 dearth of epidemiological information on seasonal influenza including its impacts (mortality,
19 attack rates, susceptibility and hospitalization) in sub Saharan African countries. The aim of this
20 review is to investigate the epidemiological burden of seasonal influenza and highlight its
21 epidemiological patterns in sub Saharan African countries. Our findings will contribute to the
22 better understanding of the burden of seasonal influenza and will be useful in the planning for
23 and response to seasonal influenza outbreaks in terms of prevention and treatment.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Methods**

44 **Patient and public involvement**

45 Patients were not involved in the design of this study.
46
47
48
49
50

51 **Eligibility criteria**

52 **Type of studies to be included**

53
54
55
56
57
58
59
60

1
2
3 Epidemiological studies conducted in sub-Saharan African countries and published between
4
5 January 1, 2000 and August 31, 2018 reporting on the burden of seasonal influenza will be
6
7 included. These dates coincides with the existence of the integrated disease surveillance response
8
9 system in Africa. We will include published estimates from studies deriving their data from
10
11 sentinel surveillance systems or healthcare facilities in which human influenza infection has been
12
13 verified using a valid laboratory test such as a reverse transcriptase polymerase chain reaction
14
15 (RT-PCR). Since influenza transmission occur throughout the tropical and sub-tropical areas in
16
17 Africa, we will consider studies with data reported weekly or monthly for at least a year. The
18
19 peak periods in influenza in the tropics are between March and September but tend to vary from
20
21 year to year depending on the type and sub-type of human influenza in circulation.¹¹⁻¹² Studies
22
23 that estimate the disease burden using modelling techniques will be excluded.
24
25
26
27
28
29
30

31 **Participants**

32
33 We will include studies that stratify influenza rates in the following age groups; 0 to <2 years, 2
34
35 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years and over 65 years. Where studies
36
37 are unable to report age stratified estimates within the proposed age groups, we will report rates
38
39 as suggested in the studies. We will pull and group similar studies together according to the
40
41 subgroup population based on the WHO case definition of influenza. The WHO case definitions
42
43 varies across age groups and across study sites. All age specific data for inclusion will be well-
44
45 defined in terms of numerators (case count) and denominators (population at risk). We will
46
47 exclude all studies that use data reported between 31 January 2009 and 1 November 2010
48
49 including all studies where study duration overlaps or combines the pandemic and non
50
51 pandemic- periods. The 2009 pandemic influenza was declared in April, 2009 and by August
52
53
54
55
56
57
58
59
60

1
2
3 2010 it was declared over.¹³ This is based on the assumption that the pandemic virus (H1N1) was
4
5 actively circulating for 6-8 weeks before and after the pandemic period.
6
7
8
9

10 **Types of outcome measures**

11
12 In order to be considered for inclusion, studies should explicitly report one or more
13
14 epidemiological burden estimates. Burden estimates refer to mortality rates, attack rates,
15
16 hospitalization or admission rates, incidence rates or period prevalence rates associated with
17
18 influenza-like illness (ILI) and severe respiratory illness (SARI). We will also adopt the
19
20 following definition of the outcome measures. Mortality rate is defined as a measure of the
21
22 number of deaths in a specific age group due to seasonal influenza divided by population of age
23
24 group expressed in 1,000 person years. Overall attack rate refers to number of new cases of
25
26 influenza during the specified time divided by the total number of specified population at start of
27
28 time interval. Age specific attack rate is calculated as a number of influenza illness among a
29
30 specified age group divided by the total number of persons in that specified age population who
31
32 were at risk to influenza at the start of the observation period. Hospitalization rate is the number
33
34 of influenza inpatient admissions discharged over a specific time and geographical area divided
35
36 by the population in that age group, expressed in terms of 1000 people days. Incidence rate is the
37
38 number of new cases per population at risk in a given time period whereas period prevalence rate
39
40 is a measurement of new and preexisting of all individuals affected by the disease over a
41
42 specified period of time divided by total number of people in that population. As far as
43
44 prevalence estimates are concerned we will only focus on period prevalence.
45
46
47
48
49
50
51
52
53

54 **Case definitions of influenza-like illness and severe respiratory illness**

55
56
57
58
59
60

1
2
3 We will adopt the WHO case definitions for ILI and SARI used between 1999 and 2018. The
4
5 1999 WHO case definition of ILI was defined as “a sudden onset of fever, a temperature $>38^{\circ}$ C
6
7 and a cough or sore throat in the absence of another diagnosis”.¹⁴ In 2018, ILI was defined as
8
9 “an acute respiratory illness with measured temperature of $\geq 38^{\circ}$ C and cough, with onset within
10
11 “10 days”.¹⁵ In 1999, SARI definition did not exist but in 2009 it was officially defined as “a
12
13 sudden onset of fever $> 38^{\circ}$ C, cough or sore throat, shortness of breath or difficulty breathing,
14
15 and requiring hospitalization. For those less than 5 years of age, pneumonia was used as criteria
16
17 including cough or difficulty breathing.¹⁶ The 2018 definition of SARI (including acute
18
19 respiratory illness (ARI), acute lower respiratory illness (ALRI) and severe or very severe
20
21 pneumonia) was “an acute respiratory illness with a history of fever or measured fever of $\geq 38^{\circ}$
22
23 C and cough, with onset within the past 10 days, requiring hospitalization.”¹⁵ We will pull studies
24
25 that report laboratory confirmed influenza in patients with pneumonia that matches the
26
27 International Classification of Disease codes (ICD-9 codes; 488.01, 488.11 and ICD-10 codes;
28
29 J09.01, J09.11, J10.0) severe illness. The WHO case definitions for ILI and SARI have changed
30
31 many times, in 2011, 2014 and 2018 in order to facility valid comparison of disease occurrence
32
33 over a period of time, and increase the sensitivity and specificity in reporting.
34
35
36
37
38
39
40
41

42 **Search method for identification of studies**

43
44 We will construct a comprehensive search strategy using key words and MESH terms in
45
46 PubMed, Embase, African Journal Online (AJOL), Cochrane, Web of science, Cinahl, and
47
48 Google scholar for relevant studies. We will conduct a database search followed by hand
49
50 searching of reference sections of all relevant studies. The medical subject heading (MeSH)
51
52 terms influenza (human) OR inter-pandemic influenza, sentinel or virologic surveillance,
53
54
55
56
57

1
2
3 mortality, morbidity, hospitalization, admission rates, clinical attack rates, Influenza Like
4
5 Illnesses (ILI) (outpatients), Severe Acute Respiratory Infections (SARI), Acute Lower
6
7 Respiratory Infections (ALRI) and Africa will be used to combine searches systematically. The
8
9 search strategy for PubMed is shown in table 1 but we plan to modify and run slightly different
10
11 search strategy across the different databases. We will not place any restriction on language but
12
13 will limit our search to studies in sub Saharan Africa.
14
15
16
17
18

19 **Selection of studies**

20
21 All the identified titles and abstracts will be examined independently for potential eligibility by
22
23 two authors (EZS and AM). Discrepancies will be resolved by consensus and if necessary by
24
25 arbitration by a third author (CSW). The full texts of potentially eligible studies will be retrieved,
26
27 and screened independently by two authors (EZS and AM). Disagreements between the first two
28
29 authors will again be resolved by discussion and consensus and by arbitration by a third author
30
31 (CSW) if necessary.
32
33
34
35
36
37

38 [Insert Table 1 here- embedded at the end of the manuscript]
39
40
41

42 **Data extraction and management**

43
44 Two study authors (EZS and AM) will extract data independently from eligible studies using a
45
46 pre-structured and tested data collection form. The information collected using this form will
47
48 include details on the year the study was conducted, setting, study design, methods, participants
49
50 and outcomes, source of funding and risk of bias. The two authors will compare the extracted
51
52 data and discrepancies will be resolved by consensus or by a third author (CSW) if relevant. In
53
54
55
56
57

1
2
3 the event where there is missing data from included studies which we deem important, we will
4
5 contact the authors of the studies involved.
6
7
8
9

10 **Risk of bias (quality) assessment**

11
12 Two independent reviewers will retrieve, screen and assess the risk of bias in the identified
13
14 studies. In context of surveillance, biases are often present at the sampling stage of
15
16 SARI/ALR/ILI case counts of which many eligible cases are excluded resulting in selection bias.
17
18 In addition, diagnostic assays used to identify cases may lead to misclassification bias. For
19
20 example, RT-PCR identifies more cases than immunofluorescence assays. The risk of bias in
21
22 prevalence studies will be assessed using the risk of bias in prevalence studies in Hoy *et al.*¹⁷
23
24
25
26
27

28 **Data and sensitivity analysis**

29
30 A descriptive analysis of the study outcomes will be undertaken if studies are not eligible to be
31
32 pooled for burden estimates. This will include studies with burden estimates that are not
33
34 representative of the catchment population. Eligible studies will be stratified by type of
35
36 population (i.e. community or hospital setting etc), surveillance type (i.e. active or passive
37
38 surveillance) and type of influenza case definitions (including whether it is based on 1999, 2014
39
40 or 2018 case definition) in order to compare similar designs. We will also stratify the burden
41
42 estimates for ILI and SARI by age or risk group. In an event there are multiple reporting in a
43
44 study we will combine all the studies or use the study with most complete dataset.
45
46
47
48

49 Quantitative estimates i.e. annual incidence, period prevalence and mortality of influenza, and
50
51 95% CIs will be obtained from all eligible studies and pooled for a statistical meta-analysis by
52
53 use of STATA software if we find that studies are similar. If burden estimates are reported by
54
55
56
57

1
2
3 week or month, we will calculate yearly burden estimates based on methods provided in the
4 WHO manual for estimating disease burden associated with seasonal influenza.¹⁸ Where studies
5 provide relevant data for the catchment population, we will pool burden proportions of all cases
6 sampled among SARI cases from whom clinical specimen were tested by week/month/year by
7 dividing the total number of SARI cases by month/week/year and multiplying it by 100%. We
8 will adjust for true total number of influenza-associated SARI cases per week/month/year by
9 scaling up the number of influenza positive SARI cases by the proportion of SARI cases tested.
10 To estimate the proportion of ILI cases attributable to laboratory-confirmed influenza illness
11 without population denominators require data on case counts (i.e. number of ILI cases positive
12 for influenza virus using laboratory tests) divided by number of ILI cases from whom clinical
13 specimens were collected for diagnostic testing multiplied by 100. To estimate number of
14 influenza-associated ILI, we will adjust the proportion influenza-associated ILI by week, month
15 or year multiplied by total number of ILI cases by week, month or year. Step by step formulas
16 are presented in in the WHO manual for estimating disease burden associated with seasonal
17 influenza.¹⁸

18
19 We will use a meta-analysis to aggregate estimate measures. The random-effects models and
20 fixed effects models of regression coefficients will be used for pooled data analysis. If necessary,
21 all studies of good methodological quality will be combined. We anticipate heterogeneity in the
22 pooled studies due to different case definitions for SARI/ILI and origin of data (active and
23 passive surveillance) thus heterogeneity will be tested using the Chi-square test and I-square test
24 statistic. We will consider a significance level of $\alpha = 0.1$ for Chi-square test and I-squared
25 statistic of >50% to reflect significant heterogeneity. Heterogeneity and non-heterogeneity will
26 be tested by deliberately dropping studies with high risk of bias from the analyses one at a time.

1
2
3 If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the
4 source of the poor data quality. We will include case definitions of influenza, passive or active
5 studies, representation of the catchment area, age, gender, seasonality (tropical or subtropical),
6 duration and type of study as covariates in the Meta analysis. Where there is significant
7 heterogeneity, meta-analysis will not be performed. Only studies with similar risk of bias
8 assessment will be pooled in a meta-analysis. We will define country burden disease estimates
9 yielded from passive sentinel surveillance data (e.g. ILI) as a lower threshold and upper
10 threshold for active sentinel surveillance data (e.g. SARI). Passive sentinel surveillance
11 substantially yields lower estimates compared to active surveillance data. A forest plot on all
12 data points and random effects estimates will be generated to give insight to the analyses. The
13 reviewers will assess the strength of the evidence according to the Grading of Recommendations
14 Assessment, Development and Evaluation (GRADE) approach.¹⁹ This approach rates the
15 strength of the evidence by taking into account five factors: methodological quality, directness of
16 evidence, heterogeneity, precision and risk of publication bias.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 **Reporting of this review**

39
40 We wrote this protocol following the Preferred Reporting Items for Systematic Review and
41 Meta-Analysis Protocols guidelines. PRISMA focuses on ways in which authors can ensure the
42 transparent and complete reporting of systematic reviews and meta-analyses.²⁰ The findings of
43 this review and any amendments will be reported according to the Preferred Reporting Items for
44 Systematic Reviews and Meta-Analyses statement.
45
46
47
48
49
50
51
52
53

54 **Ethics and communication**

1
2
3 We will conduct the systematic review and meta-analysis using the publicly available data as
4 such no formal ethical review was required. Our findings will be published in a peer review
5 journal and subsequently disseminated to policymakers through conferences and stakeholder
6 meetings.
7
8
9
10
11
12
13

14 **Data sharing statement**

15
16 Additional information beyond that contained within this manuscript can be obtained from the
17 corresponding author.
18
19
20
21
22
23

24 **Discussion and study limitations**

25
26 There is a lack of epidemiological and laboratory surveillance data on the burden of seasonal
27 influenza in Africa.²¹ This lack of information specifically attack rates, susceptibility and
28 hospitalization may undermine the role of seasonal influenza vaccination programme specifically
29 in terms of how it should be implemented. Careful understanding of seasonal influenza, through
30 continuous collection of surveillance and monitoring data of influenza activity taking place at
31 any time of the year, will assist policymakers in preparing for and to strengthening capacity for
32 seasonal influenza surveillance and reporting. The overall understanding of the burden of
33 seasonal influenza in African settings will subsequently provide information for treatment,
34 prevention and control strategies of seasonal influenza such as giving the vaccines to high risk
35 groups first. We also hope that strengthening surveillance systems for seasonal influenza that
36 report on the burden of viruses will rapidly help detect and send early signals of an impending
37 new or severe influenza activity in humans. Seasonal influenza burden estimates that provide
38 baseline data can provide valuable information with which to compare annual influenza
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 outbreaks with unusual outbreak events.¹⁸ This information can serve as a predictive indicator for
4 new events such as an influenza pandemic and systematically aid pandemic planners to plan for
5 additional capacities and resources (stockpile of antivirals and antibiotics etc) needed to deal
6 with a severity of a new pandemic activity.²²
7
8
9
10
11

12 We anticipate several limitations in our study related to bias in influenza reporting and
13 estimating burden of the disease. Firstly, pooled data from studies will be limited to respiratory
14 infections such as ILI and SARI. As such there is possibility of underestimating influenza related
15 burden caused by other clinical manifestation such as myocardial event triggered by influenza
16 infection. Secondly, ILI surveillance data do not have a known population denominators and
17 many people in the communities or catchment areas may not report influenza associated disease
18 thus making it difficult to extrapolate, for example, incidence rates. Assuming enough
19 information is provided in the studies we will adjust the estimates by using the methodology
20 provided in a similar study²³ to ours. Thirdly, while we will take precautions to review studies for
21 quality and relevance, often bias resulting from case definitions (error in coding cases),
22 diagnostic sampling and diagnostic assays are inevitable in eligible studies thus difficult to
23 determine precisely the disease burden estimations once we pool data for analyses. We
24 deliberately intend to use different WHO case definitions of SARI and ILI. However, the
25 implications of this is that much older version of case definition are highly sensitive to children
26 under age of 5 and less sensitive to older children and adults. Further implications of the use of
27 different case definitions is that pooled estimates may not be a reflection of true influenza burden
28 in the population. We intend to reconcile the different case definitions (e.g. SARI cases) in
29 different studies by matching them to hospitalized severe ALRI and pneumonia and influenza
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 (i.e. ICD-9 and ICD-10) making sure there are comparable between themselves and help in
4
5 harmonization and interpretation of data.
6
7
8
9

10 **Authors' contributions**

11
12 CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS
13
14 wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and
15
16 edited the manuscript draft and search strategy. All authors approved the manuscript.
17
18
19
20

21 **Funding statement:**

22
23 This research received no specific grant from any funding agency in the public, commercial or
24
25 not-for-profit sectors.
26
27
28
29

30 **Competing interests statement:**

31
32 None
33
34
35
36
37

38 **Patient consent:**

39
40 Not required.
41
42
43
44
45

46 **References**

- 47
48 1. World Health Organization. Influenza (Seasonal) [Internet]; c2018 [cited 2018 February/19].
49 Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/>
50
51 2. Molinari NM, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal
52 influenza in the US: measuring disease burden and costs, *Vaccine* 2007;**25**:5086-96.
53
54
55
56
57

3. Klepser ME. Socioeconomic impact of seasonal (epidemic) influenza and the role of over-the-counter medicines, *Drugs* 2014;**74**:1467-79.
4. Rüttimann RW, Bonvehí PE, Vilar-Compte D, et al. Influenza among the elderly in the Americas: a consensus statement, *Revista Panamericana de Salud Pública* 2013;**33**:446-52.
5. Cox N, Subbarao K. Global epidemiology of influenza: past and present, *Annu Rev Med* 2000;**51**:407-21.
6. Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-Saharan Africa: a systematic review, *The Lancet infectious diseases* 2011;**11**:223-35.
7. Zar HJ, Madhi SA, Aston SJ, et al. Pneumonia in low and middle income countries: progress and challenges, *Thorax* 2013;**68**:1052-6.
8. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis, *The Lancet* 2011;**378**:1917-30.
9. Nguyen-Van-Tam JS. Epidemiology of influenza, *Textbook of influenza* 1998:181-206.
10. Steffen C, Debellut F, Gessner B, et al. Improving influenza surveillance in sub-Saharan Africa, *Bull World Health Organ* 2012;**90**:301-5.
11. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions, *PLoS medicine* 2006;**3**:e89.
12. Simonsen L, Viboud C, Taylor RJ, et al. The epidemiology of influenza and its control. In: Anonymous . *Influenza vaccines for the future*: Springer 2011:27-54.
13. World Health Organisation. Pandemic (H1N1) 2009 [Internet]; c2018 [cited 2018 February/19]. Available from: <http://www.who.int/csr/disease/swineflu/en/>.
14. World Health Organization. WHO recommended surveillance standards, 1999 [Internet]; c1999 [cited 2018 February/19]. Available from: http://apps.who.int/iris/bitstream/handle/10665/65517/WHO_CDS_CSR_ISR_99.2.pdf?sequence=1&isAllowed=y
15. Fitzner J, Qasmieh S, Mounts AW, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection, *Bull World Health Organ* 2018;**96**:122.
16. Ortiz JR, Sotomayor V, Uez OC, et al. Strategy to enhance influenza surveillance worldwide, *Emerg Infect Dis* 2009;**15**:1271-8.

- 1
2
3 17. Hoy D, Brooks P, Woolf A, *et al.* Assessing risk of bias in prevalence studies: modification
4 of an existing tool and evidence of interrater agreement, *J Clin Epidemiol* 2012;65:934-9.
5
6
7 18. World Health Organization. A manual for estimating disease burden associated with seasonal
8 influenza: World Health Organization 2015 [Internet]; c2018 [cited 2018 February/19].
9 Available from:
10 http://apps.who.int/iris/bitstream/handle/10665/178801/9789241549301_eng.pdf?sequence=1
11
12
13 19. Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence
14 profiles and summary of findings tables, *J Clin Epidemiol* 2011;64:383-94.
15
16 20. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic
17 reviews and meta-analyses of studies that evaluate health care interventions: explanation and
18 elaboration, *PLoS medicine* 2009;6:e1000100.
19
20
21 21. Katz MA, Schoub BD, Heraud JM, *et al.* Influenza in Africa: uncovering the epidemiology
22 of a long-overlooked disease, *J. Infect. Dis* 2012; 206: S1–S4 21.
23
24 22. World Health Organization. Pandemic Influenza Risk Management WHO Interim
25 Guidance [Internet]; c2013 [cited 2018 February/19]. Available from:
26 [http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementI](http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf)
27 [nterimGuidance_Jun2013.pdf](http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf).
28
29
30 23. Emukule GO, Paget J, van der Velden K, *et al.* Influenza-associated disease burden in
31 Kenya: a systematic review of literature, *PloS one* 2015;10:e0138708.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7 Table 1: Search Strategy
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
 2
 3
 4
 5
 6
 7
 8
 9
 10
 11
 12
 13
 14
 15
 16
 17
 18
 19
 20
 21
 22
 23
 24
 25
 26
 27
 28
 29
 30
 31
 32
 33
 34
 35
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

(((("africa"[MeSH Terms] OR "africa"[All Fields]) AND ((((((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])) OR ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) OR ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields])) OR ADMISSION[All Fields]) OR (("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND ILLNESS[All Fields])) AND ((((((("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND LIKE[All Fields] AND ILLNESS[All Fields]) OR (SEVERE[All Fields] AND ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields])) OR (("virology"[MeSH Terms] OR "virology"[All Fields] OR "virologic"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "surveillance"[All Fields] OR "epidemiology"[MeSH Terms] OR "surveillance"[All Fields])) OR (("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields]) AND CONFIRMED[All Fields])) OR (("outpatients"[MeSH Terms] OR "outpatients"[All Fields] OR ("out"[All Fields] AND "patients"[All Fields]) OR "out patients"[All Fields]) AND VISIT[All Fields])) OR ("reverse transcriptase polymerase chain reaction"[MeSH Terms] OR ("reverse"[All Fields] AND "transcriptase"[All Fields] AND "polymerase"[All Fields] AND "chain"[All Fields] AND "reaction"[All Fields]) OR "reverse transcriptase polymerase chain reaction"[All Fields] OR ("rt"[All Fields] AND "pcr"[All Fields]) OR "rt pcr"[All Fields])) AND ((((((SEASONAL[All Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR ("human"[All Fields] AND "influenza"[All Fields])) OR (INTER[All Fields] AND ("pandemics"[MeSH Terms] OR "pandemics"[All Fields] OR "pandemic"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR (("laboratories"[MeSH Terms] OR "laboratories"[All Fields] OR "laboratory"[All Fields]) AND CONFIRMED[All Fields] AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) OR (ACUTE[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields])) OR (("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ASSOCIATED[All Fields] AND ACUTE[All Fields] AND LOWER[All Fields] AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields] OR ("respiratory"[All Fields] AND "infections"[All Fields]) OR "respiratory infections"[All Fields]))))

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only