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

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

Authors: Evanson Z Sambala[1,4], Aaron Mdolo[2,4], Richard Banda[3,4], Arthur Phiri[4], Alison B Wiyeh[1], Charles S Wiysonge[1,5,6]

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

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

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

[4] Malawi Public Health Forum, Malawi

[5]Centre 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]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

Email addresses of Authors:

Charles.Wiysonge@mrc.ac.za; Aaron.mdolo@gmail.com; Richardbanda45@gmail.com; Arthurmacphiri@gmail.com; Wberiliy@yahoo.co.uk

Corresponding Author

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

Email: Evanson_sambala@yahoo.com

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

journal and subsequently disseminated to policymakers through conferences and stakeholder meetings.

Protocol registration number: This protocol is registered with the International Prospective Register of Systematic Reviews, registration number CRD42017074091

Strengths and limitation of this study

- There is a dearth of epidemiological information on seasonal influenza in sub Saharan Africa including its impacts thus this study provides an excellent opportunity for assessment of the situation in more detail, making the proposed review relevant to inform policymakers.
- This review assess the epidemiological burdens of seasonal influenza without placing any restriction on the language in order to capture all the relevant literature.
- We anticipate a wide variation in the identified results as such pooled data will be tested for heterogeneity and non-heterogeneity by deliberately dropping one study with the most variability one at a time from the analyses.
- The overall understanding of the burdens of seasonal influenza in sub Saharan Africa will provide information for treatment, prevention and control strategies against seasonal influenza.

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

working days due to sickness, reduction in quality of life due to secondary infections, increased school absenteeism, and increased use of hospital resources.[8]

Seasonal influenza follows predictable seasonal patterns because it is caused by viruses that are already in circulation. In the northern hemisphere, seasonal influenza outbreaks occur between November and March, while in the southern hemisphere seasonal influenza occurs between April and September. Seasonal influenza activity in the tropical region is not strictly seasonal as it occurs throughout the year, with bi-seasonal peaks in summer and winter.[9 10]

The purpose of this study is synthesize the literature that have reported the burden of seasonal influenza in sub Saharan Africa.

Why is it important to do this review?

The World Health Organization (WHO) recommends reinforcement of routine epidemiological and virological surveillance in order to ensure timely detection of outbreaks and management of cases.[11] In 2002, the WHO pledged to support the Integrated Disease Surveillance Response (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of seasonal influenza. Through surveillance systems, it was anticipated that hospitals and laboratories would document useful data for assessing the burden of seasonal influenza. However, there is a dearth of epidemiological information on seasonal influenza including its impacts (mortality, attack rates, susceptibility and hospitalization) in sub Saharan African countries. The aim of this review is to investigate the epidemiological burden of seasonal influenza and highlight its epidemiological patterns in sub Saharan African countries. Our findings will contribute to the better understanding of the burden of seasonal influenza and will be useful in the planning for and response to seasonal influenza outbreaks.

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

prevalence rate is a measurement of all individuals affected by the disease at a particular times. We will exclude economic studies that report burden indicators such as financial costs associated to influenza, quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).

Data collection

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

[Insert Table 1 here- embed at the end of the manuscript]

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

Data synthesis and sensitivity analysis

A descriptive analysis of the study outcomes will be undertaken. Quantitative estimates will be obtained from all eligible studies and pooled for a statistical meta-analysis by use of STATA software if we find that studies are similar. 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. If necessary, all studies of good methodological quality will be combined. Heterogeneity will be tested using the I-squared statistic. Heterogeneity and non-heterogeneity will be tested by deliberately dropping one study with the most variability one at a time from the analyses. If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the source of the poor data quality. A forest plot on all data points and random effects estimates will be generated to give insight to the analyses.

Risk of bias (quality) assessment

Two independent reviewers will retrieve, screen and asses the risk of bias in the identified studies. The reviewers will assess the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[13] The tool encompasses six domains of which each domain include one or more specific entries in the risk table describing the study and assigning judgment relating to the risk of bias for that entry.[13] We will judge the risk of bias as either high risk, low risk or unclear risk based on the quality evidence for each study. We will develop a risk of bias table to summarize our assessments. Any disagreements or discrepancies will be resolved by discussion and if any disagreement cannot be resolved an involvement of a third reviewer will be recommended.

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

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 groups first. We also hope that strengthening surveillance systems for seasonal influenza that report on the burden of viruses will rapidly help detect and send early signals of an impending new influenza activity in humans. It can also be a predictive indicator to aid estimates of additional capacities that may be may needed to deal with a new pandemic activity in an event it occurs.[16]

Authors' contributions

CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and edited the manuscript draft and search strategy. All authors approved the manuscript.

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Competing interests statement:

None

Patient consent:

Not required.

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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

(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])))

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Authors: Evanson Z Sambala[1,4], Aaron Mdolo[2,4], Richard Banda[3,4], Arthur Phiri[4], Alison B Wiyeh[1], Charles S Wiysonge[1,5,6]

[1]Cochrane 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

[5]Centre 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.

PROSPERO registration number: CRD42017074091

Strengths and limitation of this study

- Due to the variability in the definition and diagnosis of influenza across settings and over time, there may be important differences in the case definitions (error in coding cases), diagnostic sampling and diagnostic assays from various studies. This may lead to overestimation 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
- The search for relevant studies will include both published and unpublished literature hence minimizing the risk for publication bias.

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,

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.[9]

Although much is known about the effects of seasonal influenza, including global estimates of burden of influenza, the majority of studies are derived from developed countries. The burden of seasonal influenza in Africa is not fully known. The purpose of this study is to synthesize the existing studies that have reported the burden of seasonal influenza in sub Saharan Africa.

Why is it important to do this review?

The World Health Organization (WHO) recommends reinforcement of routine epidemiological and virological surveillance in order to ensure timely detection of outbreaks and management of cases.[10] In 2002, the WHO pledged to support the Integrated Disease Surveillance Response (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of seasonal influenza. Through surveillance systems, it is anticipated that hospitals and laboratories would document useful data for assessing the burden of seasonal influenza. However, there is a dearth of epidemiological information on seasonal influenza including its impacts (mortality, attack rates, susceptibility and hospitalization) in sub Saharan African countries. The aim of this review is to investigate the epidemiological burden of seasonal influenza and highlight its epidemiological patterns in sub Saharan African countries. Our findings will contribute to the better understanding of the burden of seasonal influenza and will be useful in the planning for and response to seasonal influenza outbreaks in terms of prevention and treatment.

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

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

Types of outcome measures

In order to be considered for inclusion, studies should explicitly report one or more epidemiological burden estimates. Burden estimates refer to mortality rates, attack rates, hospitalization or admission rates, incidence rates or period prevalence rates associated with influenza-like illness (ILI) and severe respiratory illness (SARI). We will also adopt the following definition of the outcome measures. Mortality rate is defined as a measure of the number of deaths in a specific age group due to seasonal influenza divided by population of age group expressed in 1,000 person years. Attack rate refers to number of new cases of disease during specified time interval divided by the number of persons or age groups at risk in the population at the start of a time interval. Hospitalization rate is the number of influenza inpatient admissions discharged over a specific time and geographical area divided by the population in that age group, expressed in terms of 1000 people days. Incidence rate is the number of new cases per population at risk in a given time period whereas period prevalence rate is a measurement of new and preexisting of all individuals affected by the disease over a specified period of time divided by total number of people in that population. As far as prevalence estimates are concerned we will only focus on period prevalence.

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° 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 ≥ 38° 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° 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 ≥ 38° 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)

terms influenza (human) OR inter-pandemic influenza, sentinel or virologic surveillance, mortality, morbidity, hospitalization, admission rates, clinical attack rates, Influenza Like Illnesses (ILI) (outpatients), Severe Acute Respiratory Infections (SARI), Acute Lower Respiratory Infections (ALRI) and Africa will be used to combine searches systematically. The search strategy for PubMed is shown in table 1 but we plan to modify and run slightly different search strategy across the different databases. We will not place any restriction on language but will limit our search to studies in sub Saharan Africa.

Selection of studies

All the identified titles and abstracts will be examined independently for potential eligibility by two authors (EZS and AM). Discrepancies will be resolved by consensus and if necessary by arbitration by a third author (CSW). The full texts of potentially eligible studies will be retrieved, and screened independently by two authors (EZS and AM). Disagreements between the first two authors will again be resolved by discussion and consensus and by arbitration by a third author (CSW) if necessary.

[Insert Table 1 here- embeded at the end of the manuscript]

Data extraction and management

Two study authors (EZS and AM) will extract data independently from eligible studies using a pre-structured and tested data collection form. The information collected using this form will include details on the year the study was conducted, setting, study design, methods, participants and outcomes, source of funding and risk of bias. The two authors will compare the extracted

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

Risk of bias (quality) assessment

Two independent reviewers will retrieve, screen and asses the risk of bias in the identified studies. In context of surveillance, biases are often present at the sampling stage of SARI/ALR/ILI case counts of which many eligible cases are excluded resulting in selection bias. In addition, diagnostic assays used to identify cases may lead to misclassification bias. For example, RT-PCR identifies more cases than immunofluorescence assays. The risk of bias in prevalence studies will be assessed using the risk of bias in prevalence studies in Hoy *et al*.[17]

Data and sensitivity analysis

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

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

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

We will use a meta-analysis to aggregate estimate measures. The random-effects models and fixed effects models of regression coefficients will be used for pooled data analysis. If necessary, all studies of good methodological quality will be combined. We anticipate heterogeneity in the pooled studies due to different case definitions for SARI/ILI and origin of data (active and passive surveillance) thus heterogeneity will be tested using the Chi-square test and I-square test statistic. We will consider a significance level of $\alpha = 0.1$ for Chi-square test and I-squared statistic of >50% to reflect significant heterogeneity. Heterogeneity and non-heterogeneity will

be tested by deliberately dropping studies with high risk of bias from the analyses one at a time. If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the source of the poor data quality. We will include case definitions of influenza, passive or active studies, representation of the catchment area, age, gender, seasonality (tropical or subtropical), duration and type of study as covariates in the Meta analysis. Where there is significant heterogeneity, meta-analysis will not be performed. Only studies with similar risk of bias assessment will be pooled in a meta-analysis. We will define country burden disease estimates yielded from passive sentinel surveillance data (e..g. ILI) as a lower threshold and upper threshold for active sentinel surveillance data (e.g. SARI). Passive sentinel surveillance substantially yields lower estimates compared to active surveillance data. A forest plot on all data points and random effects estimates will be generated to give insight to the analyses. The reviewers will assess the strength of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[19] This approach rates the strength of the evidence by taking into account five factors: methodological quality, directness of evidence, heterogeneity, precision and risk of publication bias.

Reporting of this review

We wrote this protocol following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.[20] The findings of this review and any amendments will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

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

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

We anticipate several limitation in our study related to bias in influenza reporting and estimating burden of the disease. Firstly, pooled data from studies will be limited to respiratory infections such as ILI and SARI. As such there is possibility of underestimating influenza related burden caused by other clinical manifestation such as myocardial event triggered by influenza infection. Secondly, ILI surveillance data do not have a known population denominators and many people in the communities or catchment areas may not report influenza associated disease thus making it difficult to extrapolate, for example, incidence rates. Assuming enough information is provided in the studies we will adjust the estimates by using the methodology provided in a similar study[23] to ours. Thirdly, while we will take precautions to review studies for quality and relevance, often bias resulting from case definitions (error in coding cases), diagnostic sampling and diagnostic assays are inevitable in eligible studies thus difficult to determine precisely the disease burden estimations once we pool data for analyses. We deliberately intend to use different WHO case definitions of SARI and ILI. However, the implications of this is that much older version of case definition are highly sensitive to children under age of 5 and less sensitive to older children and adults. Further implications of the use of different case definitions is that pooled estimates may

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

Authors' contributions

CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and edited the manuscript draft and search strategy. All authors approved the manuscript.

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Competing interests statement:

None

Patient consent:

Not required.

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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 (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])))

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

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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 Phiri[4], Alison B Wiyeh[1], Charles S Wiysonge[1,5,6]

[1]Cochrane 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.

[5]Centre 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

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, 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.[9]

Although much is known about the effects of seasonal influenza, including global estimates of burden of influenza, the majority of studies are derived from developed countries. The burden of

seasonal influenza in Africa is not fully known. The purpose of this study is to synthesize the existing studies that have reported the burden of seasonal influenza in sub Saharan Africa.

Why is it important to do this review?

The World Health Organization (WHO) recommends reinforcement of routine epidemiological and virological surveillance in order to ensure timely detection of outbreaks and management of cases.[10] In 2002, the WHO pledged to support the Integrated Disease Surveillance Response (IDSR) systems which carry out monitoring and assessment of diseases, including the burden of seasonal influenza. Through surveillance systems, it is anticipated that hospitals and laboratories would document useful data for assessing the burden of seasonal influenza. However, there is a dearth of epidemiological information on seasonal influenza including its impacts (mortality, attack rates, susceptibility and hospitalization) in sub Saharan African countries. The aim of this review is to investigate the epidemiological burden of seasonal influenza and highlight its epidemiological patterns in sub Saharan African countries. Our findings will contribute to the better understanding of the burden of seasonal influenza and will be useful in the planning for and response to seasonal influenza outbreaks in terms of prevention and treatment.

Methods

Patient and public involvement

Patients were not involved in the design of this study.

Eligibility criteria

Type of studies to be included

Epidemiological studies conducted in sub-Saharan African countries and published between January 1, 2000 and August 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 exclude all studies that use data reported between 31 January 2009 and 1 November 2010 including all studies where study duration overlaps or combines the pandemic and non pandemic- periods. The 2009 pandemic influenza was declared in April, 2009 and by August

2010 it was declared over.[13] This is based on the assumption that the pandemic virus (H1N1) was actively circulating for 6-8 weeks before and after the pandemic period.

Types of outcome measures

In order to be considered for inclusion, studies should explicitly report one or more epidemiological burden estimates. Burden estimates refer to mortality rates, attack rates, hospitalization or admission rates, incidence rates or period prevalence rates associated with influenza-like illness (ILI) and severe respiratory illness (SARI). We will also adopt the following definition of the outcome measures. Mortality rate is defined as a measure of the number of deaths in a specific age group due to seasonal influenza divided by population of age group expressed in 1,000 person years. Overall attack rate refers to number of new cases of influenza during the specified time divided by the total number of specified population at start of time interval. Age specific attack rate is calculated as a number of influenza illness among a specified age group divided by the total number of persons in that specified age population who were at risk to influenza at the start of the observation period. Hospitalization rate is the number of influenza inpatient admissions discharged over a specific time and geographical area divided by the population in that age group, expressed in terms of 1000 people days. Incidence rate is the number of new cases per population at risk in a given time period whereas period prevalence rate is a measurement of new and preexisting of all individuals affected by the disease over a specified period of time divided by total number of people in that population. As far as prevalence estimates are concerned we will only focus on period prevalence.

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° 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 ≥ 38° 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° 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 ≥ 38° 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) terms influenza (human) OR inter-pandemic influenza, sentinel or virologic surveillance,

mortality, morbidity, hospitalization, admission rates, clinical attack rates, Influenza Like Illnesses (ILI) (outpatients), Severe Acute Respiratory Infections (SARI), Acute Lower Respiratory Infections (ALRI) and Africa will be used to combine searches systematically. The search strategy for PubMed is shown in table 1 but we plan to modify and run slightly different search strategy across the different databases. We will not place any restriction on language but will limit our search to studies in sub Saharan Africa.

Selection of studies

All the identified titles and abstracts will be examined independently for potential eligibility by two authors (EZS and AM). Discrepancies will be resolved by consensus and if necessary by arbitration by a third author (CSW). The full texts of potentially eligible studies will be retrieved, and screened independently by two authors (EZS and AM). Disagreements between the first two authors will again be resolved by discussion and consensus and by arbitration by a third author (CSW) if necessary.

[Insert Table 1 here- embeded at the end of the manuscript]

Data extraction and management

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

the event where there is missing data from included studies which we deem important, we will contact the authors of the studies involved.

Risk of bias (quality) assessment

Two independent reviewers will retrieve, screen and asses the risk of bias in the identified studies. In context of surveillance, biases are often present at the sampling stage of SARI/ALR/ILI case counts of which many eligible cases are excluded resulting in selection bias. In addition, diagnostic assays used to identify cases may lead to misclassification bias. For example, RT-PCR identifies more cases than immunofluorescence assays. The risk of bias in prevalence studies will be assessed using the risk of bias in prevalence studies in Hoy *et al*.[17]

Data and sensitivity analysis

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

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

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

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

If statistical heterogeneity is present, a subgroup analyses will be undertaken to examine the source of the poor data quality. We will include case definitions of influenza, passive or active studies, representation of the catchment area, age, gender, seasonality (tropical or subtropical), duration and type of study as covariates in the Meta analysis. Where there is significant heterogeneity, meta-analysis will not be performed. Only studies with similar risk of bias assessment will be pooled in a meta-analysis. We will define country burden disease estimates yielded from passive sentinel surveillance data (e..g. ILI) as a lower threshold and upper threshold for active sentinel surveillance data (e.g. SARI). Passive sentinel surveillance substantially yields lower estimates compared to active surveillance data. A forest plot on all data points and random effects estimates will be generated to give insight to the analyses. The reviewers will assess the strength of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[19] This approach rates the strength of the evidence by taking into account five factors: methodological quality, directness of evidence, heterogeneity, precision and risk of publication bias.

Reporting of this review

We wrote this protocol following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.[20] The findings of this review and any amendments will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

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.

Data sharing statement

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

Discussion and study limitations

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 groups first. We also hope that strengthening surveillance systems for seasonal influenza that report on the burden of viruses will rapidly help detect and send early signals of an impending new or severe influenza activity in humans. Seasonal influenza burden estimates that provide baseline data can provide valuable information with which to compare annual influenza

outbreaks with unusual outbreak events.[18] This information can serve as a predictive indicator for new events such as an influenza pandemic and systematically aid pandemic planners to plan for additional capacities and resources (stockpile of antivirals and antibiotics etc) needed to deal with a severity of a new pandemic activity.[22]

We anticipate several limitations in our study related to bias in influenza reporting and estimating burden of the disease. Firstly, pooled data from studies will be limited to respiratory infections such as ILI and SARI. As such there is possibility of underestimating influenza related burden caused by other clinical manifestation such as myocardial event triggered by influenza infection. Secondly, ILI surveillance data do not have a known population denominators and many people in the communities or catchment areas may not report influenza associated disease thus making it difficult to extrapolate, for example, incidence rates. Assuming enough information is provided in the studies we will adjust the estimates by using the methodology provided in a similar study[23] to ours. Thirdly, while we will take precautions to review studies for quality and relevance, often bias resulting from case definitions (error in coding cases), diagnostic sampling and diagnostic assays are inevitable in eligible studies thus difficult to determine precisely the disease burden estimations once we pool data for analyses. We deliberately intend to use different WHO case definitions of SARI and ILI. However, the implications of this is that much older version of case definition are highly sensitive to children under age of 5 and less sensitive to older children and adults. Further implications of the use of different case definitions is that pooled estimates may not be a reflection of true influenza burden in the population. We intend to reconcile the different case definitions (e.g. SARI cases) in different studies by matching them to hospitalized severe ALRI and pneumonia and influenza

(i.e. ICD-9 and ICD-10) making sure there are comparable between themselves and help in harmonization and interpretation of data.

Authors' contributions

CSW, ABW, EZS, AM, AP and RB contributed to the conceptualization of the review. EZS wrote the manuscript draft. EZS, ABW developed the search strategy. All authors revised and edited the manuscript draft and search strategy. All authors approved the manuscript.

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Competing interests statement:

None

Patient consent:

Not required.

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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 (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])))