INPLASY PROTOCOL

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None declared.

Epidemiology and effectiveness of interventions for Foot and Mouth Disease in Africa: A protocol for systematic review and meta-analysis

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Review question / Objective: **What is the epidemiology and effectiveness of control measures for foot and mouth disease in African countries?' PICOS: Description of elements Population/ problem/Setting: Artiodactyla (cloven ungulates), domestic (cattle, sheep, goats, and pigs), camels and wildlife (buffaloes, deer, antelope, wild pigs, elephant, giraffe, and camelids) affected by Foot and Mouth Disease (FMD) or Hoof and Mouth Disease (HMD) caused by the Foot and Mouth Disease Virus (FMDV) in Africa. Intervention: Prevention measures: vaccination, 'biosafety and biosecurity', sensitization of the public. Control measures: quarantine, movement control, closure of markets and stock routes, mouth swabbing of animals with infected materials (old technique that is no long applicable), culling, mass slaughter, stamping out and any other interventions or control measures generally accepted by the 'community of practice' of animal health practitioners. Comparator: areas that did not have any control activities for FMD, in head-to-head comparisons in the same study. Outcome: epidemiological outcomes: incidence, prevalence, patterns or trends, clinical symptoms, and risk factors. Effectiveness outcomes: success, and usefulness of the interventions measured as averted deaths, illness and infections, and costs associated with the interventions (cost–effectiveness). Study design: epidemiological designs include cohort design for incidence, cross sectional for prevalence and case-control for clinical symptoms and risk factors. Interventional designs include randomized controlled trials, cluster randomized trials, quasi-experimental designs – controlled before and after, interrupted time series, [regression discontinuity design, difference-in-difference, and propensity score matching]. Timelines: 1900 – 2022.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 November 2022 and was last updated on 09 November 2022 (registration number INPLASY2022110039).

INTRODUCTION

Review question / Objective: **What is the epidemiology and effectiveness of control measures for foot and mouth disease in African countries?' PICOS: Description of elements Population/ problem/Setting: Artiodactyla (cloven ungulates), domestic**

(cattle, sheep, goats, and pigs), camels and wildlife (buffaloes, deer, antelope, wild pigs, elephant, giraffe, and camelids) affected by Foot and Mouth Disease (FMD) or Hoof and Mouth Disease (HMD) caused by the Foot and Mouth Disease Virus (FMDV) in Africa. Intervention: Prevention measures: vaccination, 'biosafety and biosecurity', sensitization of the public. Control measures: quarantine, movement control, closure of markets and stock routes, mouth swabbing of animals with infected materials (old technique that is no long applicable), culling, mass slaughter, stamping out and any other interventions or control measures generally accepted by the 'community of practice' of animal health practitioners. Comparator: areas that did not have any control activities for FMD, in head-to-head comparisons in the same study. Outcome: epidemiological outcomes: incidence, prevalence, patterns or trends, clinical symptoms, and risk factors. Effectiveness outcomes: success, and usefulness of the interventions measured as averted deaths, illness and infections, and costs associated with the interventions (cost–effectiveness). Study design: epidemiological designs include cohort design for incidence, cross sectional for prevalence and case-control for clinical symptoms and risk factors. Interventional designs include randomized controlled trials, cluster randomized trials, quasi-experimental designs – controlled before and after, interrupted time series, [regression discontinuity design, difference-in-difference, and propensity score matching]. Timelines: 1900 – 2022.

Rationale: There is no systematic review that has been conducted on the epidemiology and effectiveness of interventions to control FMD globally let alone in Africa. A quick and clean search in PubMed, using the keyword search "Foot and Mouth Disease" and "animal", revealed 3,333 articles, with 422 non – systematic reviews and 5 systematic reviews on various topic regarding FMD on 20th July 2022. These systematic reviews covered priority setting for animal health (Ref), duration of infection stages (Mardones et al., 2010), challenges of simulation models of FMD (Pomeroy et al., 2017), and methods to analyze FMD economic impact (Compston et al., 2022); and (Zaheer et al., 2020) leaving out the epidemiology and effectiveness of interventions, the subject of our proposed systematic review. Further, despite the different control measures employed, FMD continues to occur in several countries, especially in the sub-Saharan Africa. This raises concern as to why the control measures have not been effective, something that this review seeks to find an answer to by synthesizing the available evidence from the different existing single studies. Such information will guide policy development on the control of the disease, farm practices, and future research. Specifically, this review will form the baseline used by researchers, academia, technocrats, and implementors of policies on how effectively we need to control and prevent further occurrence of the disease.

Condition being studied: Foot and mouth disease (FMD) is a highly infectious and contagious viral disease caused by Foot and Mouth Disease Virus (FMDV) (OIE, 2012). FMD is a transboundary disease and trade-sensitive disease that affects both the national and international trade of animals and animal products. FMD affects divided-hoofed (cloven-hoofed) domestic and wild animals including cattle, sheep, goats, pigs, camels, and buffaloes (OIE, 2012). The FMDV is a single-strand plus sense ribonucleic acid (RNA) virus of the family Picornaviridae and the genus Aphthovirus made up of 8500 bases of four structural proteins (Grubman and Baxt 2004; Arber, 1977; Sáiz et al., 2002). FMDV has seven immunologically distinct serotypes: O; A; C; Southern African Territory (SAT1, SAT2, and SAT3); and Asia1 which offer no cross-immunity against each other. The FMDV is known for forming vesicles in the epithelial tissues around the mouth, feet, and mammary glands of affected animals (Paton et al., 2018). The FMDV is spread by direct and indirect routes, the direct transmission involves contamination with aerosol and contact through fomites. The indirect route occurs through contact and secondary aerosols by

contaminated animal products (Paton et al., 2018; Brown et al., 2022). The clinical disease is characterised by; fever; blisters on the feet, mouth, nose, muzzle, and teats. There is also lameness, salivation; reduced appetite due to painful blisters in the mouth, milk drop and weight loss; abortions; death in young animals, and a naïve susceptible population (OIE, 2012). The disease is given named "foot and mouth disease" based on the most common signs of lameness and excessive salivation caused by blisters and matching of the mouth. The disease can be prevented by early detection (Pacheco et al., 2017), diagnosis, and surveillance (Arjkumpa et al., 2020). There are several interventions have been employed to respond to FMD outbreaks. The common ones are vaccination, quarantine, animal movement restrictions, aphthisation, closure of livestock markets and trade routes, observing biosecurity and biosafety measures, culling, stamping out, creation of awareness, and sensitization of the public. Globally, FMD was present in 77% of the global livestock population and was endemic in Asia, Africa, and the Middle East. The countries that were free of the disease by 2022 included: Australia, New Zealand, Indonesia, Central, and North America, and continental Western Europe (OIE, 2012). Foot and mouth disease causes both direct and indirect economic losses (Knight-Jones & Rushton., 2013; Baluka, 2016). The global economic loss due to FMD was estimated to be around US$6.5 and 21 billion in the endemic regions and more than US$1.5 billion per year in the FMD-free countries and zones (Knight-Jones and Rushton, 2013).

METHODS

Search strategy: This systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for protocols (PRISMA-P) guideline (Moher et al., 2009).

Data sources - Data will be obtained by performing an electronic search by the lead reviewer (RM) under the guidance of an Information Science Specialist and systematic review expert (AK). The following databases will be searched:

1. PubMed: https://pubmed.ncbi.nlm.nih.gov/
2. Web of Science: https://www.webofscience.com
3. Medline: https://www.nlm.nih.gov/medline/medline
4. Vet Med Resources: https://www.cabi.org/vetmedresource/
5. Google Scholar: https://scholar.google.com/

The electronic data search - This will be done guided by the 'PICO' elements. The following terms will be combined and searched in the PubMed database using the following categories:

Terms describing the population affected by the disease and the disease-causing agent: 'Foot and Mouth Disease', FMD, 'Hoof and Mouth Disease', HMD, 'Foot and Mouth Disease Virus', FMDV, 'Hoof and Mouth Disease Virus', HMDV;

Terms describing and animals affected: artiodactyla, artiodactyls, 'cloven ungulates', 'domestic animals', cattle, sheep, goats, pigs, wildlife, buffaloes, deer, antelope, wild pigs, elephant, giraffe, and camelids.

Terms describing the interventions under study: vaccinations, quarantine, 'movement control, 'market closure', 'stock route closure', screening, 'mouth swabbing', 'biosafety and biosecurity', 'infection control', 'community sensitization', 'public engagement', 'culling', 'slaughter', 'stamping out'.

Terms describing the relevant outcomes: epidemiology, incidence, prevalence, spread, effectiveness, control, 'control program', illness, sickness, death, 'cost–effectiveness',

These terms will be expounded by their synonyms and Medical Subject Headings (MeSH terms) then combined using Boolean operators (AND, OR, NOT) as appropriate. Truncation, abbreviations, and proximity searching will be applied to improve the search accuracy.

The filter will be done for the time period from 1900 to 2022. This search will be piloted and refined in consultation with the co-authors.

Article eligibility and screening - The articles identified from the different databases will be exported into EndNote (version X9) referencing software for screening. The duplicates will be removed, then a pair of reviewers (RM and a research associate) will scrutinize the title and abstract. This being a doctoral project, only one pair of reviewers will perform data collection and analysis, with guidance from the senior reviewers (RA, EN, EAO, MO). Initially, the primary reviewer (RM) will perform duplicate screening with one of the senior reviewers (RA) to pilot the eligibility criteria for 50 articles. The relevant and eligible full articles will be obtained for data extraction with the guidance of the Librarian (AAK). Any disagreements in eligibility will be resolved by consensus and validated by any content experts (JM, SNB, AEO).

Inclusion criteria - The articles that meet the "PICO" criteria will be included. In addition, included articles would have reported the history of the disease; or reported at least one outcome of relevance whether epidemiological or effectiveness as appropriate. Effectiveness studies will be included only if they reported a comparison group.

Exclusion criteria - Articles will be excluded if they are totally irrelevant not meeting any of the PICO criteria or were conducted Africa. In addition, studies will be excluded if they meet part of the PICO criteria yet reported hand, foot and mouth disease (HFMD), or were designed for methodological investigations, early phase vaccine development, laboratory experiments, diagnostic accuracy studies, treatment trials, or marketing of drugs and vaccines.

Data extraction and management - A pair of reviewers will perform data extraction independently and in duplicate. The primary reviewer (RM) with support from one senior reviewer (RA) will in duplicate abstract data for 10 articles, to pilot the data abstraction tool. Data extraction by use of any appropriate open-access software tool will be explored in the pilot phase. The data extracted will include: the title, objectives of the study, lead author, year of publication, the year when the study was conducted, country, region, test, species of animals, study design, sample size, number positive, prevalence, type of interventions or control measures studied, serotypes, outcomes reported, risk factors and link to the article. The outcomes will include measures of effectiveness, changes in FMD viral infections, illness, or deaths; and other economic outcomes such as drop-in beef or milk production, associated costs, and cost-effectiveness.

Participant or population: This review will focus on cloven animals both domestic and wildlife susceptible to foot and mouth disease. The domestic animals are cattle, sheep, goats, pigs, camels, and buffaloes. The wildlife animals include deer, African buffaloes, antelopes, and wild pigs.

Intervention: The following are the interventions for the control of FMD: quarantine, movement control, closure of markets and stock routes, mouth swabbing of animals with infected materials (aphthisation), culling, mass slaughter, stamping out, and any other interventions or control measures generally accepted by the 'community of practice' of animal health practitioners.

Comparator: Not applicable.

Study designs to be included: Cross-sectional, surveys, cluster analysis, longitudinal, molecular, phylogenetic analysis, case-control, cohort studies, retrospective.

Eligibility criteria: Article eligibility and screening The articles identified from the different databases will be exported into EndNote (version X9) referencing software for screening. The duplicates will be removed, then a pair of reviewers (RM and a research associate) will scrutinize the title and abstract. This being a doctoral project, only one pair of reviewers will perform data collection and analysis, with guidance from the senior reviewers (RA, EN, EAO, MO). Initially, the primary reviewer (RM) will perform duplicate screening with one of the senior reviewers (RA) to pilot the eligibility criteria for 50 articles. The

relevant and eligible full articles will be obtained for data extraction with the guidance of the Librarian (AAK). Any disagreements in eligibility will be resolved by consensus and validated by any content experts (JM, SNB, AEO). Inclusion criteriaThe articles that meet the "PICO" criteria will be included. In addition, included articles would have reported the history of the disease; or reported at least one outcome of relevance whether epidemiological or effectiveness as appropriate. Effectiveness studies will be included only if they reported a comparison group. Exclusion criteriaArticles will be excluded if they are totally irrelevant not meet any of the PICO criteria or were conducted in Africa. In addition, studies will be excluded if they meet part of the PICO criteria yet reported hand, foot and mouth disease (HFMD), or were designed for methodological investigations, early phase vaccine development, laboratory experiments, diagnostic accuracy studies, treatment trials, or marketing of drugs and vaccines.

Information sources: Handling missing data from included studies 'NR' will be used to denote that are needed but whose information is missing or not reported. These will be clarified by contacting the available authors. We shall not conduct any statistical analysis on variables described as missing or not reported.

Main outcome(s): The success and usefulness of the interventions are measured as averted deaths, illnesses and infections, and costs associated with the interventions (cost-effectiveness).

Additional outcome(s): Absence or disappearance of the disease after the implementation of the interventions.

Data management: A team of reviewers about ten in number with experience in systematic review and meta-analysis will be comprised. They will be involved in drafting the title, formulation of the PICOS frammework, screening of papers, extraction of the data, development and validation of research question, eligibility criteria, search strategy, identification and searching of the different databases, development of search library, exporting to an excel sheet, protocol writing and registration, title and abstract screening, full-text screening, data extraction, quality assessment of the different papers, statistical analysis, meta-analysis, double checking of everything, drafting and writing of a manuscript, identification of possible journal for submission, revision of the manuscript and final submission, dissemination of the findings.

Quality assessment / Risk of bias analysis: JBI's critical appraisal tools assist in assessing the trustworthiness, relevance, and results of published papers (Munn et al., 2015).

Strategy of data synthesis: Data will be synthesized using structured narrative synthesis, descriptive statistics, and followed by quantitative meta-analysis.

Subgroup analysis: Meta-Analysis will be done for the articles that describe the epidemiology of the disease in terms of the seroprevalence i.e. number sampled, numbers seropositive, and pooled seroprevalence. Subgroup analysis in terms of the species of animals (cattle, goats, sheep, buffaloes, and camels), then according to the regions of Africa (Eastern, Western, Northern, Central, and Southern regions) will be obtained. MetaXL version 5.6 will be used.

Sensitivity analysis: Forest, funnel and Doi plots will be used for sensitivity analysis.

Language restriction: English.

Country(ies) involved: Africa.

Other relevant information: Not applicable.

Keywords: Foot and Mouth Disease; Epidemiology; Interventions; Effectiveness; Africa.

Dissemination plans: The findings will be disseminated through different fora to academicians, policymakers, political and

technical leaders, farmers, technical staff, and the general public. The review team will organize appropriate fora for the dissemination of findings.

Contributions of each author:

Author 1 - Robert Mwebe - Developed the research topic, wrote the original protocol and is the primary reviewer.
Email: rmwebe@gmail.com
Author 2 - Chester Kalinda - Expert in systematic review and Meta-analysis; proved the skills of review and will approve the final manuscript.
Email: ckalinda@gmail.com
Author 3 - Ekwaro A. Obuku - Helped to modify the topic, secondary reviewer.
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Author 4 - Eve Namisango - Helped to modify the topic, secondary reviewer.
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Author 5 - Alison A. Kinengyere - Helped to modify the topic; further development of the search strategy, data screening, and extraction.
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