Indigenous Groups and Influenza: Protocol For A Systematic Review and Meta-Analysis

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Protocol

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Abstract

Background: Several studies have documented that indigenous groups have been disproportionally hit by previous pandemics, with some exceptions. The objective of this review and meta-analysis is to provide a comprehensive historical overview of pre-COVID impact of influenza on indigenous groups by combining data from the last five influenza pandemics and seasonal influenza up to date.

Methods/Principle Findings: The review will include peer-reviewed original studies published in English, Spanish, Portuguese, Swedish, Danish and Norwegian. Records will be identified through systematic literature search in eight databases: Embase, Medline, Cinahl, Web of Science, Academic Search Ultimate, SocIndex, ASSIA and Google Scholar. Results will be summarized narratively and using meta-analytic strategies.

Discussion: To our knowledge, there is no systematic review combining historical data on the impact of both seasonal and pandemic influenza on indigenous populations. By summarizing results across indigenous groups in different countries and historical periods, we aim to provide information on how strong the risk for influenza is among indigenous people, and how consistent this risk is across groups, areas and time.

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Introduction

In 2020, Indigenous people comprised 6% of the world's population with an estimated 476 million people (1). History has shown that indigenous groups may be disproportionally affected by diseases such as influenza and be more likely to experience severe outcomes compared to non-indigenous counterparts (2).

Although a vaccine preventable disease, influenza remains one of the world's greatest public health challenges. Every year, there are an estimated 1 billion cases of seasonal influenza, of which 3-5 million are severe cases, leading to 290,000-650,000 deaths globally (3-5). The 2009 "swine flu" pandemic resulted in an estimated 60 million cases, 274,304 hospitalizations, and 12,469 deaths in the USA alone (6). Such morbidity and mortality figures result in a huge economic burden due to direct health care spending and indirect costs, such as loss of productivity as a consequence of workplace absenteeism stemming from employees' own sickness or care for others (7-10). One hundred years ago, the "Spanish Flu" pandemic of 1918-20 took the lives of ~50 million people globally (2.5%). Influenza pandemics have appeared 3-4 times each century since the first documented pandemic in 1510 (11), and it is not a matter of whether we will have another influenza pandemic in the near future post COVID-19 – the question is when and if it will be devastating (as in 1918) or rather mild (as in the recent 2009 pandemic). A severe pandemic akin to the 1918 influenza could lead to 80 million deaths and cost as much as 5% of the global GDP, nearly USD 4 trillion (12). Subsequent, less severe pandemics occurred in 1957-58, 1968-69, and 2009-10, resulting in-4 millions, 1-4 million and 100,000-400,000 global deaths (13).

Multiple studies report raised risks of adverse medical outcomes for indigenous groups during influenza pandemics. For example, in the 1918 pandemic the indigenous Māori on New Zealand and the Sami population in Norway had respectively 4-6 and 7 times higher mortality risks than non-indigenous counterparts (14, 15). These risk disparities appears persistent across time and space. In the 2009 pandemic, indigenous people in North America, Oceania and the Pacific had 3–8 times higher pandemic mortality than the majority populations (16, 17). Studies of indigenous populations in North America and Oceania find raised risk for severe disease and death both today and 100 years ago (16-25).

The reasons for these ethnic disparities are complex, poorly understood, and represent an area of limited research. Genetic, epidemiological and social science research is also carried out in silos. Influenza research on indigenous groups, including research on influenza preparedness planning, often focus on specific areas such as North America (26) or Oceania (27), adding to the fragmented silo-understanding.

Influenza-related ethnic disparities in the 2009 influenza pandemic may be explained in part by a higher prevalence (2–7 times higher) of risk factors for severe influenza outcomes among the indigenous (e.g., diabetes mellitus, obesity, asthma, chronic obstructive pulmonary disease and a greater number of pregnancies at young age). Less documented factors include those associated with the risk of infection (e.g. crowding, family size and poverty), differences in access to health care, and a greater genetic susceptibility (19). Finally, the fact that Indigenous populations have historically been isolated means that their immunological imprinting and lifetime experience with influenza is almost certainly important too. Indigenous populations in the USA, Canada (28), and Australia (29, 30), but not New Zealand, are prioritized for both seasonal and pandemic influenza vaccines, and would have been targeted also in 1918 if effective vaccines had been available (31). However, although being a target group for vaccination, additional reasons for the disparities may be that indigenous groups tend to have lower vaccination rates than white majority populations (19, 32, 33).

Although outside the scope of this research, there is support that this raised vulnerability of indigenous people also appears for pandemics not involving influenza, such as COVID-19 (34-36). Nevertheless, there are studies showing specific countries and historical periods in which indigenous groups were protected of disproportionate morbidity or mortality (36). Such cases may be particularly important to identify, in that they may indicate the presence or absence of factors influencing the risk disparities faced by indigenous groups that can be utilized in pandemic planning to reduce these disparities.

In this study, we present the first systematic review and meta-analysis on the association between indigenous background and influenza, focusing on both seasonal influenza and the last five pre COVID-19 influenza pandemics (1889, 1918, 1957, 1969, 2009) with the following review question: How strong is the association between indigenous background and influenza outcomes, and is the association strong enough to be important for prevention policy, i.e. above and beyond the role of medical risk factors?

Methods

This protocol is in line with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement (37) (see checklist Additional file 1). The protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42021246391) (38).

Systematic literature search

The searches were conducted during January and February 2021 in eight databases: Embase, Medline, Cinahl, Web of Science, Academic Search Ultimate, SocIndex, ASSIA and Google Scholar. The search strategy was developed and piloted in collaboration with research librarians to combine sensitivity and precision. Searches were conducted according to PICO-criteria (39). The result of the piloted tests was that the final search strategy was comprised of two elements and their synonyms and related terms: indigenous peoples and influenza. These terms with synonyms were combined within each database (see Additional file 2 for search strategy). No language nor publication data restrictions were applied at this stage. Two reviewers screened abstracts, and then all included full-text studies independently with the software Covidence (40). Upon completion of screening in Covidence, we will screen the reference lists of included studies and relevant reviews on the topic for additional eligible studies not retrieved by our search.

Eligibility criteria for title and abstract screening

The types of influenza covered in this protocol are seasonal influenza up to literature search date and the last five pre-COVID-19 influenza pandemics, which occurred during 1889, 1918, 1957, 1969 and 2009. We will include quantitative studies statistically investigating the relationship between indigenous (versus non-indigenous) background and disease outcome (morbidity, hospitalization and mortality). The relationship between indigenous background and influenza must be empirically investigated and reported in full-text articles in peer-reviewed journals. Indigenous background was captured by key words such as native, aboriginal, Sami, etc. (see Additional file 2 for more examples). Morbidity was captured by key words such as infection rates, transmission rates, lab confirmed influenza, flu like illness, and influenza like illness (ILI). Severe disease was captured by key words such as disease severity, critical illness, critical disease, severe illness, severe disease, hospitalization, patient admission, hospital admission, intensive care unit (ICU) admission, and ICU treatment. Mortality was captured by key words such as fatal outcome, fatal illness, fatal disease, fatality, lethal outcome, lethal illness, lethal disease, terminal outcome, terminal illness, terminal disease, lethality, death, death rate, and mortality rate. All these key words were used in both pilots and the final search as described above. Studies covering both seasonal and pandemic influenza and distinguishing between non-pandemic and pandemic years will be included. We will also include studies of vaccine efficacy on influenza outcomes that also include indigenous status as covariate controls. Study language must be English, Danish, Norwegian, Swedish, Spanish and

Portuguese to generate manageable results. Two independent reviewers will screen studies independently and discuss until they reach consensus.

Exclusion criteria for title and abstract screening

Exclusion criteria are: 1. Reviews, theoretical and policy-oriented papers that do not utilize original empirical data. 2. Studies that only include different indigenous groups, without comparing them to their respective national majority group. 3. Studies on pandemic diseases other than influenza (e.g., COVID-19). 4. Studies on both seasonal and pandemic influenza that did not distinguish between non-pandemic and pandemic years. 5. Studies on influenza vaccine uptake, attitudes towards influenza vaccination and compliance with (non)pharmaceutical interventions during seasonal influenza or pandemics. 6. Case studies or qualitative studies on the associations between indigenous background and seasonal influenza and pandemic outcomes. 7. Studies on social justice and influenza. 8. Studies of pandemic influenza preparedness plans.

Data selection and extraction

We will extract the following data from included studies:

1. Article info
    a. First author
    b. Year published
    c. Journal
2. Data sample
    a. Country or region of analysis
    b. Seasonal years up to January 2021 (data search conduction) or pandemic years (1889, 1918, 1957, 1968, 2009)
    c. Sample inclusion criteria – i.e. characteristics of indigenous sample/population and of the majority reference group (age-group/median/average, age, gender, patient group, civilian, military, pregnant, etc).
    d. Sample size
    e. Unit of analysis (individuals, households, regions, hospitals etc)
    f. Data aggregation level (observations of individual units, aggregated units, etc.). e.g., if hospitals are the unit of analysis, does the data used occur at the hospital level or is it pooled across hospitals?
    g. Source of outcome data, e.g., census, routine notification data (e.g. influenza cases reported to a doctor), survey data, register data etc.

h. If survey or population data had incomplete coverage

i. Response rate/coverage

ii. Representativity: Is the sample shown to be representative for the population? i.e. has a non-response analysis been carried out?

3. Outcome variable - Pandemic outcome (a. morbidity, b. hospitalization, c. mortality)

a. Definition of morbidity: influenza-like illness (ILI), Lab-confirmed Infection rates (PCR), transmission rates (reproduction number, R0), immunity/antibodies towards influenza (HI titer above a certain threshold) due to exposure to the disease and not vaccination

b. Definition of hospitalization; Hospitalized inpatients with (PCR) or without confirmed influenza; patients admitted to intensive care unit (ICU) or not; mechanically ventilated patients ("lung machines") or not; inpatients vs outpatients

c. Definition of cause of mortality: Influenza and pneumonia (PI), excess mortality (PI, all causes of death etc.), respiratory diseases, pneumonia etc.

4. Baseline outcomes (control type), i.e. what was the control group or baseline outcome comparison? (general healthy population, infected patients, the hospitalized, patients with lab-confirmed seasonal influenza)

5. Independent variables of interest – indigenous group(s) definition versus majority group definition (register, self-report, etc).

6. Statistical methodology

a. Design of study (cross sectional, longitudinal, case-control, cohort studies)

b. Estimation technique (Cross tables, correlation analysis, OLS, Poisson regression, Logistic regression, Cox regressions, GEE regressions, GLMM models etc.)

c. Control variables included (e.g. age, gender, SES indices, marital status, pre-existing disease, health behavior etc.) in light of sample restrictions (e.g. for pregnant women, gender is not among the controls). SES indices include education, income, crowding, density, deprivation index, unemployment, occupational social class, poverty status, % below poverty level)

d. Reference categories with which all point estimates are compared

7. Results reported (separate spreadsheet).

Data synthesis

Before meta-analysis, we plan to conduct narrative analysis based on the main outcomes by (non)indigenous status and groups. We plan to use an adapted version (41) of the Effective Public Health Practice Project (EPHPP) checklist for risk of bias and quality assessment. If EPHPP is not precise or sensitive enough for our study results, we will select another appropriate tool for quality assessment. At

least two reviewers will assess the overall quality of each study based on study design, sample size, participation rate, attrition and results. Discussions will be used to resolve discrepancies, if any.

A narrative synthesis will summarize findings according to study characteristics of the included studies, such as seasonal/pandemic years, study region (region/country/hospital), indigenous sample and majority reference sample, sample size, unit of outcomes, data aggregation level, data sources and type, outcomes, baseline outcomes, design, statistical techniques, controls and whether the study estimates are used in the meta-analysis, and whether (specific) indigenous background is an independent predictor.

Meta-analysis

Two meta-analytic techniques will be used to summarize the findings. The studies included assess risk discrepancies in different periods, for different diseases, for different indigenous groups. Considering this, a random effects meta-analytic model will be used to allow for effect heterogeneity. The random effect model allows the study-level effects to differ from each other and estimates the underlying effect variation. The simpler “fixed effect” model, on the other hand, requires the assumption that the true risk discrepancy estimated (with noise) by the individual studies is the same across all studies. This is unlikely to be appropriate in our context, where studies using different indicators of indigenous background and flu outcomes in data from different countries and time-periods that allow for different levels of confounder control, majority reference background, etc.

The random effect model will be estimated on the full set of studies with comparable outcome measures (e.g., log odds-ratios and relative risk measures). We will also perform split sample analyses to assess how similar results are within subgroups of studies grouped by region, period/pandemic and indigenous background.

A risk with such split-sample analyses is that they compare smaller groups, giving less precise estimates and a higher risk of “false positive” differences in subgroup results. In addition, they do not account for the correlations between the characteristics used to define subgroups. If studies of a specific group tend to come from a specific pandemic period, and if these results also differ from those of other studies, this would affect both the sub-sample analysis comparing different groups, as well as those splitting by period.

Based on prior experience with meta-analysis in a related context (42), we will consequently also use a Bayesian meta-analytic model to assess how estimates vary with study-level indicators and the type of comparisons made. This model allows us to include multiple distinctions simultaneously (e.g., indigenous group, period, region), using a hierarchical specification to reduce the risk of overfitting. If the evidence indicates that estimates vary no more across study level indicators than we would expect due to sampling variation, then this will pull the individual indicator coefficients towards zero. The Bayesian model also includes a prior distribution for the parameters, which can be used to express plausible beliefs regarding the parameter values before running the analysis, further reducing the risk that weak tendencies

in the data result in inflated estimates. In brief, a hierarchical specification and the use of a prior biases the results slightly towards zero and “no group differences” – but increases precision by down-weighting implausible and non-credible effect estimates and group differences.

Discussion

To understand the effect of influenza on indigenous people, we need to consider more than biology, and include social, economic and political factors embedded. Both the immediate (local) and the distal/political (regional and national) environments surrounding indigenous groups appear to impact how hard particular indigenous people, within a specific region with certain national guidelines, are protected during a pandemic (36). History can inform us about past experiences with pandemics, which for some groups are connected to painful memories, and even near-extinction or collective trauma. Some Amerindian groups have been completely exterminated by outside diseases like smallpox or measles, while others have barely survived after death rates worse than the medieval plague (43). It is therefore not surprising that new pandemics might revive painful memories, or even trauma, among those with indigenous backgrounds. Indigenous vulnerability cannot be isolated to biology or indigenous culture, without taking into account their regional and national context, including the degree of national preparedness, extent of collaborative responses between governments and indigenous groups.

Some studies have suggested that co-participation of indigenous groups in governmental strategies to reduce disease outbreaks may be of special importance. As is trust in regional health services that are culturally sensitive, and affordable (44). In a recent review (45), countries that were successful in protecting their whole population from the COVID-19 pandemic, were also those successful in protecting their indigenous groups. These countries also used their knowledge about past pandemics, such as the 2009 pandemic which disproportionately hit indigenous groups, to cooperate with indigenous representatives in order to engage with indigenous groups to spread information and reduce infections.

Results from our systematic review and meta-analysis, will enable the assessment of the amount of variation in influenza outcomes among indigenous groups across regions and time since the 1889 pandemic. In addition, we expect to identify studies with deviating results (extraordinarily high or low estimations) which may indicate specific factors that could be of political relevance to reduce risk disparities among indigenous groups.

Declarations

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Availability of data and materials

Not applicable

Authors' contributions

DEA has contributed to the writing of this protocol, the PROSPERO-protocol, as well as design adaptations linked to eligibility and exclusion criteria. SEM has contributed to the design, grant applications that resulted in funding and writing the protocol. OR has designed and written the plan for data synthesis and meta-analysis. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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