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Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review

PROTOCOL

Health Protection Research Group, Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, UK

A project commissioned by the World Health Organisation

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Background

Influenza viruses with potential to cause pandemics are currently notifiable under the International Health Regulations (IHR) if at least two of the following conditions are observed; a) the disease caused is detrimental to the individual's health, b) the event is unexpected or with an unusual presentation, c) there is the risk of international spread and d) the international spread is likely to result in the implementation of travel and trade restrictions at international level (1).

Different preventative and containment strategies have been devised by WHO since 2005 for implementation at national and international level in the eventuality of an influenza pandemic scenario (2). The interventions considered include thermal and symptom screening of travellers at entry and exit of countries, imposition of travel restrictions and ban of movement of people into and from infected regions and countries, isolation and quarantine measures (2). Under IHR, countries are expected to develop the capacity to deal with the risk of international spread of diseases at designated points of entry (e.g. ports, airports and ground crossings) (1). In 2009, the WHO reinforced previous recommendations by promoting the integration by its member states of interventions as part of National rapid containment strategies (3).

In the same year, a global pandemic state was declared by WHO, after human-to-human transmission of H1N1 influenza was confirmed and outbreaks at community level were observed in several countries across different WHO regions (3). Global travel played an important role in the dissemination of the pandemic in 2009.

There is currently scarce evidence of the efficacy of travel restrictions in the containment and delay of spread of pandemic influenza (4). It is therefore relevant to assess quantitatively the impact of internal and international travel restrictions in its containment, as those are currently part of WHO's pandemic preparedness and response guidance (3).

A recent systematic review in 2009 assessed travel restrictions against the potential pandemics by influenza viruses in combination with other intervention strategies (e.g. hand hygiene, personal protection, social distancing) (5). Travel restrictions were found to have limited impact in the containment of spread of influenza and were most efficacious when used in combination with other interventions (5). Jefferson and colleagues have reported in

a recent systematic review assessing the impact of control measures against respiratory viruses that in most studies evaluated did not assess appropriately the efficacy of border controls and that there was a lack of evidence that needed to be addressed (4). However this systematic review did not included travel restrictions amongst the interventions assessed.

This protocol describes the methodology that will be followed for undertaking a systematic review to assess the effectiveness of travel restrictions in the rapid containment of a potential influenza pandemic. For this purpose, relevant literature covering travel restriction aspects of pandemic influenza, and seasonal human influenza will be considered. The systematic review will be conducted according to the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (6). The University of Nottingham was commissioned by the World Health Organization Global Influenza Programme (WHO GIP) to undertake this work.

The protocol here presented will be registered and available through the International Prospective Register of Systematic Reviews, (http://www.crd.york.ac.uk/Prospero/), also known as PROSPERO. The upload of the protocol will take place before the literature search strategy is executed. The protocol may be subjected to further modifications if deemed necessary; updated versions of the protocol will be uploaded accordingly on PROSPERO.

Research questions

The objective of this systematic review is to assess the efficacy of international and internal (domestic) travel restrictions pursuant to its use in Rapid Containment of pandemic influenza. As necessary, this will incorporate literature on these interventions generally in interruption of spread of influenza across and within borders. The question that will be considered for the purpose of this systematic review is:

1. What is the impact of domestic travel restrictions (including travel bans) on the spread of human influenza within and between countries?
2. What is the impact of international travel restrictions (including travel bans) on the spread of human influenza within and between countries?

The characteristics of the population, intervention(s), comparator(s) and outcomes to be assessed were defined according to the PICO statement in Table 1 (6):

Table 1- Description of the population, intervention(s), comparator(s) and outcome(s) (PICO) that will be used for the purpose of the systematic review.

PICO	Description
Population	People of any given age or gender travelling by air, terrestrial or maritime means from, to or within affected countries with pandemic influenza or seasonal influenza.
Intervention	Travel restrictions between and/or within countries implemented upon any means of transport either by air, land or sea.
Comparator(s)	Existence of a comparator in a study will not be considered as a pre-requisite for inclusion in the systematic review, as it is likely that many of the studies of interest will not include a comparator by design. Where available, studies with comparators will also be considered. Therefore, studies with comparators such as countries or territories without international and/or internal travel restrictions against pandemic influenza or human influenza will be assessed.
Outcome(s)	Measurement of overall effectiveness of international and/or internal travel restrictions on the containment and/or spread (transmission) in populations within a country (e.g. domestic spread) and between countries (e.g. international spread), respectively. The measurement parameters considered will include; odds ratio, relative risk, basic reproduction number or R_0 within and across populations, prevalence, morbidity rate, mortality rate, incidence rate, cumulative incidence, attack rate, delay of spread or delay of peak of epidemic (i.e. measured in days/weeks/months) or other valid quantitative measurement methods where applicable.

Study selection

Eligibility criteria for inclusion used in this study will be as follows:

- Historical reports, reviews, systematic reviews, meta-analyses and mathematical modelling studies assessing the overall effectiveness of travel restrictions in the

prevention and/or rapid containment of spread of pandemic influenza and seasonal influenza.

- Observational (e.g. case-control, prospective and retrospective cohort, cross-sectional studies) and experimental studies describing the effectiveness of overall border controls in the prevention and rapid containment of spread of pandemic influenza and seasonal influenza.
- No restrictions have been made on the population or extract of the population considered in terms of age, gender or health status.
- No restriction on type of means of transportation (e.g. aerial, terrestrial, maritime) used and on type or level of travel restrictions imposed to contain pandemic influenza adopted at national and/or international level. Migratory movements (e.g. immigration and emigration) were also considered for the purpose of this study.
- Studies that include data referring to one or several (if not all) of the outcomes here described; a) impact of travel restrictions assessed on the incidence rate of pandemic influenza, b) impact of travel restrictions assessed on the risk of transmission and spread of the pandemic, c) impact of travel restrictions on the occurrence of new outbreaks or new cases, within a country or between regions within a country (e.g. internal borders).
- Full text manuscripts of papers that are published in English, Spanish, French and Italian will be included. At a preliminary stage, only abstracts available in English will be considered. If studies reported in other languages are found to be relevant after careful evaluation of the abstract, these will be considered after selection of a translator or colleague from that “mother tongue” is identified through WHO.

Exclusion criteria used for the purpose of this study will be as follows:

- Any type of study or part of a study that included the evaluation of effectiveness of travel restrictions assessing introduction and/or spreading of influenza through the

movement of animals and/or products of animal origin or in which the outcome relates to disease in animals but not in humans.

- Any literature or search result which does not describe quantitatively findings of outcome measures obtained from an experimental study, observational study, mathematical modelling study, systematic review (± meta-analysis) or historical report.
- Any systematic review (± meta-analysis) which has been superseded by an updated evidence synthesis (such as updated reviews published by the Cochrane Library).

The search criteria were initially piloted by two researchers prior to the preparation of this protocol to generate the final search strategy. The final search strategy will be conducted by Ana Mateus (AM), Harmony Otete (HEO) and Charles R. Beck (CRB). All identified studies and other relevant literature will be screened by two researchers for eligibility using a three-stage sifting approach to review the title, abstract and full text. When in presence of complex literature, this will be reviewed also by a third researcher. The number of documents identified and screened out will be recorded at each stage and presented accordingly in a PRISMA diagram. Reasons for exclusion will be disclosed during the process. Any disagreements will be resolved by discussion or by involvement of a third reviewer, if deemed necessary.

Assessment of risk of bias and data extraction

Bias will be assessed following the criteria stipulated by the PRISMA statement (6). For this effect, bias in individual studies will be assessed at a) study (i.e. large reporting of small against large scale studies), and b) outcome (i.e. selective reporting) levels.

The Cochrane Collaboration tool (7) will be used to assess risk of bias at study and outcome levels in experimental and prospective cohort studies. In observational studies, the Newcastle-Ottawa Scale (NOS) will be used instead (8). Risk of bias in included systematic reviews will be evaluated through the US Agency for Healthcare Research Quality (AHRQ) domain and element-based evaluation instrument (http://www.ahrq.gov/) (9).

Funnel plots of effect size versus sample size and Egger's regression test will be conducted to assess quantitatively publication bias when and if meta-analysis is conducted. Additionally, heterogeneity across studies will be assessed quantitatively with the I-square test as part of the meta-analysis process.

Potential bias in the reporting of outcomes will be assessed in all studies using the quality assessment tools mentioned above. Furthermore, any confounding derived from the risk of selection bias will be assessed in non-randomised studies as per recommendations of the Cochrane Collaboration (http://www.cochrane.org/). Bias in non-randomised studies may contribute to the occurrence of heterogeneity between studies. Reviewers will be required to describe characteristics of study design and statistical analysis used by researchers to control selection bias in each study. Data will be extracted in duplicate independently by two reviewers from the selected literature through the use of an excel template. The template will be piloted for validation and quality purposes. The same revised version of the template will be used throughout the systematic review process for consistency purposes. Data will be extracted according to the PICO framework shown in appendix 1. If required, data will be reviewed and/or discussed with another reviewer within the research group (AM, CRB, HEO, GD, JVT).

Confounding factors reported and methods used to minimise those in each study will be noted by reviewers. In compliance with the Cochrane Collaboration, below is a list of potential confounding factors anticipated to be of importance in the present review (determined based on expert opinion within the review team):

- Demographic characteristics of the study population
- Setting(s) from which study population has been sampled
- Comparator (e.g. other intervention or no intervention) used in the study
- Methodology used to assess study outcome measures
- Assumptions (input data) in mathematical modelling studies
- Quality (accuracy) of input data used in mathematical modelling studies
- Mathematical models presented without sensitivity analysis

Literature regarding mathematical models used to evaluate effectiveness of border control interventions will be assessed and described in a separate section. This is due to the current lack of validated instruments to assess quality of evidence presented in mathematical models. A qualitative assessment of those will be conducted taking into account criteria currently used for the critical appraisal and design of mathematical models (10). The qualitative assessment will cover the following aspects:

- Research question(s) posed and level precision/ clarity.
- Primary findings of the study presented.
- Originality of findings obtained.
- Model techniques used for the purpose of the study.
- Model structure used (e.g. explanatory diagram and/or equations presented for clarification?)
- Appropriateness of model complexity (e.g. does the model incorporates the most important determinants of transmission and relevant data sources).
- Suitability of mathematical modelling to explore the research question (e.g. if not appropriate, what other methods should have been used for this effect?).
- Identification of data sources used as input in the models.
- Description and explanation of major model assumptions.
- Factors explored through the model.
- Methodology used for model validation.
- Techniques used for model fitting.
- Description and suitability of sensitivity analysis used (if any; if none were used, are there any explanations provided by authors).

Data synthesis

Study characteristics (e.g. study design, interventions evaluated, sample size, sampling methods amongst others) and outcome(s) of interest will be described and summarised in tables accordingly. To synthesise the data extracted and evaluate its quality a narrative

approach will be used according to the framework described by the Economic and Social Research Council and recommended by the University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/) (11). This will be used to; a) build a theory of how, why and for whom the intervention(s) work; b) develop a preliminary synthesis of findings of the integrated studies, c) investigate relationships within and between studies and d), evaluate the degree of robustness of the synthesis.

Meta-analyses of pooled estimates of effect size (including 95% confidence intervals) and tests for heterogeneity may be conducted as part of the systematic review process depending on the suitability and quality of the eligible literature, resources available and timescale of the systematic review. Sub-group and sensitivity analysis may be carried out to assess the quality of input data extracted and its impact on the precision and estimation of the effectiveness of the interventions of interest (11).

Dissemination

A final report based on the findings of the systematic review will be submitted to WHO. It is anticipated that the report will be adapted into a manuscript for the purpose of scientific publication in a peer-review journal.

An oral presentation of this work may be delivered to WHO GIP (planned date: 12th of April 2013).

An abstract may be submitted for presentation of the systematic review findings (± meta-analysis) at appropriate health protection and/or infectious disease conferences during 2013/14.

Resources implications

The project lead and the senior supervisor will work closely with the WHO coordinator to define the scope and methods of the systematic review as a dynamic process. The WHO coordinator will aid in the retrieval of unpublished scientific research and in the identification of individuals with scientific background that can act as translators and/or assessors of literature in any other language than those specified in the criteria specified in

the section “Study selection” in this protocol. Timescales and key milestones will be agreed between the senior supervisor, the project lead and the WHO coordinator. These will be adjusted and/or modified as deemed necessary based on the data availability, data quality and resources available.

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Appendix 1- Literature search strategy

Listing of search terms based on the Medical Subject Headings (MeSH) and associated free text that will be used for the purpose of the systematic review.

Area	MeSH thesaurus headings	Free text
Population	Persons	People OR person OR subject* OR individual* Men OR women Patient Health OR healthy Neonat* OR infant Child OR children Young OR adolescen* OR adult* OR elder* OR old*
	Disease	Disease OR diseased OR ill* OR illness OR risk
	Paediatrics	Paediatr* OR pediatr*
	geriatrics	Geriatr*
	Travel	Travel* Border* sea or maritime or cruis* or boat* or ship* terrest* OR land air or aircraft or airplane* or airport* or flight* or plane* Port
	Human migration/ emigration and immigration	Migrat* emigrat* OR immigrat* settlement* or resettlement*
	Refugees	Refugee*
Intervention(s)		Restrict* OR prohib* OR ban OR bann* OR clos*
Comparator(s)		No AND (restrict* OR prohib* OR ban OR bann* OR clos*)
Outcome(s)	Pandemics	Pandemic*
	disease transmission, infectious	Transmi* OR spread OR infection* OR infected OR "person to person" OR "person-person" OR "person-to-person" OR populat* OR communit*

		control OR controlled OR contain* domestic* OR state* OR provinc* OR region OR regional* OR countr* OR nation* OR internation*
	disease outbreaks	Outbreak*
	basic reproduction number	R_0

Influenza terms	**MeSH thesaurus headings**	**Free text**
	Influenza, Human Influenza A Influenza B	Flu OR influenza influenza OR flu OR (influenza AND like) OR influenza-like OR (flu AND like) OR flu-like OR ILI or grippe Influenza AND human

MeSH thesaurus headings and free text terms listed above may be amended in order to make these compatible with databases which do not use MeSH or cover mainly non-English language literature. As such, for those equivalent and/or translated terms will be used where deemed necessary. Search interfaces with limited functionality (e.g. those which support single line searches only, limited number of search terms, etc) may be initially searched using broad influenza-specific terms followed by longer search strings or by using "advanced search" modalities if these are available in the interfaces used.

Search limits stipulated for the purpose of the systematic review.

Limit category	**Specified limit**
Languages	English, Spanish, Portuguese, Italian, French. Literature in other languages will be considered for inclusion based on relevance and resources available.
Publication type	No restriction.
Date of publication	Limit date until the end of December 2012 for all type of studies considered.
Study design	Studies without identified comparator(s) will be included when deemed relevant.
Other limits	Only human data will be considered.

Any searches of the literature and criteria used must be documented at all times to allow replication of the methodology used. Free text searches shall cover both title and abstract, when the latter is available. Searches must include MeSH thesaurus headings and free text terms that cover PICO criteria (e.g. population, interventions, comparator and outcomes). The free terms and MeSH headings shall be combined with the Boolean operator OR and/or can be combined with AND, at a later stage of the search process, following these 2 steps; (1) population AND intervention AND outcomes (PIO) AND influenza terms, (2) population AND intervention AND comparator AND outcomes (PICO) AND influenza terms. The combinations of search terms across the PICO groups will be extracted separately to produce the final list of search hits from each database. All search hits should be imported into reference management software to collate the identified literature. All duplicates will be removed prior to the 3rd stage sifting process electronically via the reference software. Duplicates will be removed by other means (e.g. manually by the reviewer), if importing of the search hits into the reference management software is not viable.

Below is the list of potential data sources, medical databases and organisations that will be explored for the purpose of the systematic review.

Category	Sources
Healthcare databases	MEDLINE EMBASE CINAHL Cochrane Library (CENTRAL) PubMed (includes MEDLINE) WHO Global Index Medicus
Evidence-based reviews	Bandolier Cochrane Library (CDSR, DARE, NHS HTA database)
Guidelines	NHS Evidence (NHS Clinical Knowledge Summaries and the National Library of Guidelines) Department of Health (DH) CDC guidance
Grey literature	Web of Science NHS Evidence (evidence summaries, grey literature, diagnostic tests, health technology assessments, primary research, and systematic reviews) OpenSIGLE (system for information on grey literature in Europe) Consultation with domain experts– Richard J Pitman (Oxford Outcomes, Oxford, UK) Peter Grove (DH, UK) Martin Cetron (CDC, US) John Edmunds (London School of Hygiene and Tropical Medicine)
Hand searching of relevant journals	Eurosurveillance (ECDC), Emerging Infectious Diseases (CDC)
Reference tracking	Reference lists of all studies selected for inclusion will be searched to identify further relevant studies
Citation tracking	Web of Science (Science Citation Index) Google Scholar
Internet searching	www.google.com www.dh.gov.uk www.hpa.org.uk

	www.who.int www.cdc.gov www.flu.gov

An example of a search output is presented below using PubMed as the source database.

Number	Search terms	Hits
1	Persons[MeSH Terms]	7130003
2	Patient OR health OR healthy OR neonat* OR infant OR child OR children OR young OR adolescen* OR adult* OR elder* OR old* OR men OR women OR people OR person OR subject* OR individual*	10963336
3	Disease[MeSH Terms]	112454
4	Disease OR diseased OR ill OR illness OR risk	4066436
5	Pediatrics[MeSH Terms]	40883
6	Paediatr* OR pediatr*	530185
7	Geriatrics[MeSH Terms]	26075
8	Geriatr*	102385
9	Travel[MeSH Terms]	19208
10	Travel*	45584
11	Human migration[MeSH Terms]	22298
12	Migrat*	192813
13	(Emigration and immigration[MeSH Terms])	22285
14	Emigrat* OR immigrat*	30486
15	Settlement* or resettlement*	7810
16	Refugees[MeSH Terms]	6260
17	Refugee*	8147
18	Border*	82643

19	Air or aircraft or airplane* or airport* or flight* or plane*	358724
20	Terrest* or land	42625
21	Sea or maritime or cruis* or boat* or ship*	77493
22	Port OR ports	23784
23	1-22	12306094
24	(Flu OR influenza) AND #23	50812
25	Restrict* OR prohib* OR ban OR bann* OR clos*	1005328
26	Pandemics[MesH Terms]	2258
27	Pandemic*	14733
28	Disease transmission, infectious[MeSH Terms]	46896
29	Transmi* OR spread OR infection* OR infected OR "person to person" OR "person-person" OR "person-to-person" OR populat* OR communit*	3016971
30	Epidemics[MeSH Terms]	3398
31	Epidemic*	68480
32	Disease outbreaks[MeSH Terms]	62261
33	Outbreak*	85120
34	Control OR controls OR controll* OR contain*	4485735
35	Domestic* OR state* OR provinc* OR region OR regional* OR countr* OR nation* OR internation*	6888011
36	26-35	10672507
37	Influenza A virus[MeSH Terms]	27826
38	Influenza B virus[MeSH Terms]	2726
39	Influenza, human[MeSH Terms]	31836
40	Influenza OR flu OR (influenza AND like) OR influenza-like OR (flu AND like) OR flu-like OR ILI or	75570

	grippe	
41	36 AND 40	59406
42	23 AND 25 AND 36 AND 40	5871
43	PIO: 23 AND 25 AND 36 AND [influenza, human (MESH)]	3244