

Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—International Travel-Related Measures

Sukhyun Ryu, Huizhi Gao, Jessica Y. Wong, Eunice Y.C. Shiu, Jingyi Xiao, Min Whui Fong, Benjamin J. Cowling

International travel–related nonpharmaceutical interventions (NPIs), which can include traveler screening, travel restrictions, and border closures, often are included in national influenza pandemic preparedness plans. We performed systematic reviews to identify evidence for their effectiveness. We found 15 studies in total. Some studies reported that NPIs could delay the introduction of influenza virus. However, no available evidence indicated that screening of inbound travelers would have a substantial effect on preventing spread of pandemic influenza, and no studies examining exit screening were found. Some studies reported that travel restrictions could delay the start of local transmission and slow international spread, and 1 study indicated that small Pacific islands were able to prevent importation of pandemic influenza during 1918–19 through complete border closure. This limited evidence base indicates that international travel-related NPIs would have limited effectiveness in controlling pandemic influenza and that these measures require considerable resources to implement.

From time to time, novel influenza A virus strains emerge and cause global influenza pandemics (1). Pandemics occurred 3 times in the 20th century and 1 time so far in the 21st century (2). The recognition that influenza pandemics can have substantial social and economic effects in addition to the impact on public health, along with the emergence of highly pathogenic strains of avian influenza virus in the past 20 years, has stimulated greater attention in preparing for future influenza pandemics (3,4). Given the delays in the

availability of specific vaccines and limited supplies of antiviral drugs, nonpharmaceutical interventions (NPIs) form a major part of pandemic plans (2).

A range of NPIs can be applied at international, national, and local levels, with the objectives of delaying the arrival of infected persons, slowing the spread of infection, delaying the epidemic peak, and reducing the size of the peak (5). This article focuses on the use of measures related to international travel, including entry and exit screening of travelers for infection, travel restrictions, and border closures (Table 1). We aimed to review the evidence base assessing the effectiveness of these travel-related NPIs against pandemic influenza and to identify the barriers to implementation of these interventions.

Methods and Results

We searched for literature reporting or estimating the effectiveness of NPIs related to international travel and movement, including entry and exit screening travelers, travel restrictions, and border closures on pandemic or interpandemic influenza. We conducted literature searches on PubMed, Medline, Embase, and Cochrane Library for peer-reviewed articles published from January 1, 1946, through April 28, 2019. The search terms used were identified from relevant systematic reviews and research reports (8,9). We collected additional studies from secondary references from included studies or other relevant searches. Articles were eligible for inclusion if they reported or estimated the effectiveness of international travel–related NPIs for pandemic influenza using quantitative indicators such as delaying the introduction of infection, delaying the epidemic peak, or reducing the size of the peak. We excluded

Author affiliations: University of Hong Kong, Hong Kong, China (S. Ryu, H. Gao, J.Y. Wong, E.Y.C. Shiu, J. Xiao, M.W. Fong, B.J. Cowling); Konyang University, Daejeon, South Korea (S. Ryu)

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Table 1. Terminology of international travel-related nonpharmaceutical interventions

| Screening travelers | International travel restriction | Border closure |
|---|--|---|
| Screening travelers entering or leaving a country for signs and symptoms of influenza virus infection or recent exposure to influenza virus infection by using health declaration forms, visual inspections, thermal scanners, or any combination of these measures (6) | Limitations on travel between particular countries (7) | Complete prevention of movement of individuals into and out of a particular country (7) |

articles if they did not investigate the quantitative effectiveness of international travel-related NPIs or were editorials, reviews, or commentaries without primary data. Furthermore, we restricted articles to those published in English. Two independent reviewers (S.R. and H.G.) screened titles and abstracts and assessed full-text articles for eligibility. A third reviewer (B.J.C.) adjudicated any disagreements between the 2 reviewers.

We extracted the information on the effectiveness of NPIs from included studies by using a structured data-extraction form. Information of interest included the study setting, specific measures implemented, timing of intervention implementation, study results regarding effectiveness indicators, and potential barriers to implementation. The assessment of quality of evidence considered study design and assigned generally higher quality to randomized trials, lower quality to observational studies, and lowest quality to simulation studies. We provide full search terms, search strategies, selection of articles, and summaries of the selected articles (Appendix, <https://wwwnc.cdc.gov/EID/article/26/5/19-0993-App1.pdf>).

Screening Travelers for Infection

We identified 4 relevant studies that considered the effect of screening on influenza transmission, including 2 epidemiologic studies from the 2009 pandemic (10,11) and 2 simulation studies (12,13). The epidemiologic studies estimated that entry screening delayed the arrival of influenza A(H1N1)pdm09 virus to previously unaffected areas by an average of 7–12 days (11) and delayed the epidemic in China by 4 days by reducing imported cases by 37% from border entry screening (10). The simulation studies predicted that entry screening would delay the arrival of infection into a country by a few days or 1–2 weeks at most (12,13). We did not identify any studies on exit screening; in the 2009 influenza pandemic, exit screening was not implemented by Mexico (14), nor by most other countries.

We did not systematically review studies of the technical performance of various screening tools (e.g., screening case definitions and thermal scanners) but identified in an informal search 4 studies that

discussed the challenges of screening travelers for infection, which include limited screening sensitivity (10,11,13), an incubation period of 1–7 days for influenza A(H1N1)pdm09 virus (meaning some infected travelers might not show symptoms until after arrival at their destination) (10,12,13), limited local capacity of influenza surveillance (10,11), and limited public health resources, such as laboratory capacity and funding (10,11,13).

Screening inbound travelers for infection is a very visible public health intervention and can reduce the number of infectious persons entering the country (15). Infrared thermometers are currently used in many ports of entry in Asia because of the instantaneous and noninvasive nature of their use. Several simulation studies (10–13) included in this review estimated that this intervention helped to delay the introduction of infected persons. However, the sensitivity of screening travelers has been largely reliant on the sensitivity of detection of fever. Epidemiologic studies (16,17) conducted during the 2009 influenza pandemic demonstrated the low detection rate of entry screening that used the infrared thermal scanner and health declaration form at the airport; the sensitivity of screening travelers for infection was 5.8% in New Zealand and 6.6% in Japan. In addition to the lack of sensitivity for detecting febrile travelers (e.g., some travelers with febrile illness might take antipyretic medicine and evade detection), some infected travelers might travel during the incubation period, which is typically 1–2 days, and thus would not be identified as infected at departure or arrival (10,12). Once infection begins spreading in a local community, identifying additional inbound travelers with infection will do little to limit local spread. In addition, entry screening consumes considerable public health resources, including trained staff, screening devices, and laboratory resources, and thus might not be justifiable (18).

Travel Restrictions

We identified 1 epidemiologic study and 9 simulation studies that estimated or predicted the effectiveness of international travel restrictions (19–28) (Table 2). An epidemiologic study estimated that the peak

in the number of influenza-associated deaths was delayed by 2 weeks when international flight volume was reduced by 27% (28). Simulation studies predicted that 90%–99% of travel restrictions could delay international spread of cases by 2–19 weeks (20), delay the importation of the first case-patients by 1–8 weeks (23–26), and delay the epidemic peak by 1–12 weeks (19,23,24,26,27).

A simulation study predicted that selectively restricting the travel of children could delay the spread

of infection by 35 days ($R_0 = 1.2$ – 2.0) (22), and another simulation study assessing the probability of escaping 1918–19 influenza pandemic among 17 Pacific Island countries and territories estimated that 4–5 countries avoided influenza pandemic ($R_0 = 1.5$ – 3.0) by strict limitation (79% or 99% restriction) of incoming travelers (21). Three studies explored the barriers to travel restrictions, which included the threat of economic loss (21,26) and lack of compliance among the public (20).

Table 2. Overall summary of effectiveness international travel-related non-pharmaceutical interventions for reducing influenza transmission

| Objective | Screening travelers | Travel restriction | Border closure |
|-------------------------------|--|---|---|
| Delaying introduction of case | <ul style="list-style-type: none"> Likely delay by 4 d with detection rate of 37% travelers identified from the port of entry at the border (10)* Associated with mean additional delay of case importation (7–12 d, 95% CI 0–30days, 2009 H1N1 pandemic) (11)* Might delay 3 d reaching 20 infected cases at risk-country ($R_0 = 1.5$ with 400 travelers/day) (12) Might delay importation of infected case-patients (21–1555 d, 2009 H1N1 pandemic) (13) | <ul style="list-style-type: none"> The mean time delays for exporting the infected case is 5.3 d (80% restriction), 11.7 d (90%), and 131.7 d (99%) ($R_0 = 1.8$ with implementation of 20 d from first case occurred) (20)* Among 17 Pacific Island countries and territories, with 99% restriction, 6 countries (with $R_0 = 1.5$) and 4–5 countries (with $R_0 > 2.25$) would likely escape the pandemic influenza with >50% probability (implemented at very beginning of pandemic) (21) Full children-selective travel restriction might delay an epidemic by 19–35 d ($R_0 = 1.2$), and less than 15 d ($R_0 = 1.6$ and 2.0, implemented after pandemic declared) (22) Mean delay of the first imported case in influenza-affected countries was estimated <3 d (40% restriction), and ≈2 weeks (90% restriction) with $R_0 = 1.7$ and implementation after pandemic declared (23) Likely delay interval between first global case and the importation of the first cases by 7–37 d ($R_0 = 1.4$, 1.7, or 2; 90% or 99% restriction; implemented 30 d after first global case occurrence) (24) Might delay the first passage time of infected case-patient from 18 d to 31 d (outbreak originated from Hong Kong) and from 7 d to 27 d (from Sydney) with $R_0 = 1.7$ (25) A 99% restriction of air-only, both air and land, and all modes of transportation might delay the interval between the first imported case and 100 infected case-patients passed the border by a week, 1–2 weeks, and 2 mo, respectively ($R_0 = 1.4$; implemented on the day after the first global case reported) (26) | <ul style="list-style-type: none"> Arrival of influenza pandemic was significantly delayed and reduced compare with the other Pacific Island Jurisdictions (29)* |
| Delaying the epidemic peak | <ul style="list-style-type: none"> Not available | <ul style="list-style-type: none"> Imported infections might delay the epidemic peak of the United States by 1.5 wks (90% restriction), 3 wks (99%), or 6 wks (99.9%) with $R_0 = 1.4$–2.0 (implemented 30 d into global pandemic) (19) Might delay pandemic peak by 6–39 d ($R_0 = 1.4$, 1.7, or 2; 90% or 99% restriction; implemented 30 d after first global case occurrence) (24) Might delay epidemic peak by 2 wks (99% air travel restriction), 3.5 wks (99% air and land travel restriction), and 12 wks (99% all mode of transportation) with $R_0 = 1.4$ (26) Might delay median epidemic peak by 7–102 d ($R_0 = 1.8$–5; 50%–99.9% restriction) (27) Peak of influenza mortality delayed by 2 wks (27% international flight volume reduction) (28) | <ul style="list-style-type: none"> Not available |
| Reducing the size of the peak | <ul style="list-style-type: none"> Not available | <ul style="list-style-type: none"> Not available | <ul style="list-style-type: none"> Not available |

*Epidemiology study.

Because the volume of transportation is associated with the spread of influenza (28,30), travel restrictions have been considered as a measure to reduce international spread (31). Although previous expert survey and reviews suggested that travel restrictions are less likely to be effective (8,9,32), international travel restrictions are still included in some national pandemic plans (33). Several of the studies we reviewed (19,20,22–28) predicted that international travel restrictions might delay the importation of new infected persons from other affected areas, slow the international spread of the epidemic, and delay the epidemic peak (25). However, simulation studies estimated that travel restrictions after 5 months of the international arrival of the first infected persons would not be effective (26) and that only strict travel restriction was likely to be effective (19); thus, the time of implementation of this measure should be considered with strict travel restrictions at the early stage of a pandemic. Some barriers exist to implementation of travel restrictions against pandemic influenza, most notably the potential economic consequences of restricting business travelers, as well as legal and ethical issues regarding mobility restrictions (34), discrimination of persons from influenza-affected area (35), and lack of public compliance.

Border Closures

One study investigated the effectiveness of border closures in 11 South Pacific Island jurisdictions during the 1918–19 influenza pandemic. We identified 4 islands where strict border control, including 5–7 days of maritime quarantine, substantially delayed the importation of influenza from 3 to 30 months and reduced the mortality rate compared with the other islands that had not implemented border control (36).

Because travel can drive cross-border transmission of infectious diseases, complete border closure could in theory prevent or delay the spread of influenza or its introduction in previously unaffected countries (21,36). However, in practice, complete border closure is likely to be unfeasible, even on isolated islands, because of the need to import food and medical supplies (21), and would result in substantial economic and social disruption (34).

Discussion

We reviewed the effectiveness of each international travel-related NPI and the barriers to its implementation to provide scientific evidence to public health authorities. Our review found that the effect of screening travelers on entry to a country or region is very limited and unlikely to be a rational use of resources.

However, this intervention has a potential role to inform travelers about the risk for infection and provide travel advice on avoiding travel to certain regions after departure or how to seek treatment after arrival (16). Furthermore, such screening can be seen by policy makers and politicians as a visible public health measure to help assure the public that action is being taken (16).

Our review identified the potential threat of economic consequences as a major barrier to implementation of travel restrictions. A simulation study demonstrated that children-selective travel restriction during a pandemic is less likely to affect economic impact compared with nonselective travel restrictions (22). A more structured epidemiologic study is needed to examine the cost and benefit of travel restriction by different risk groups of influenza transmission. A previous study demonstrated that successful border closure for 6 months in an island country provided a net societal benefit of USD 7.3 billion (36). However, this extreme measure is unlikely to be implemented unless required by national law in extraordinary circumstances during a very severe pandemic. The literature on border closure included in our review was based on the historical scenario of the 1918–19 influenza pandemic in isolated islands; this research might have limited relevance given the current and ever increasing levels of globalization.

Although international travel-related NPIs are not likely to be able to prevent importation of pandemic influenza to a country or region, NPIs implemented at the early phase might delay the start of a local epidemic by a few days or weeks (37), which is important if such delay can contribute to reducing the effect of the epidemic (e.g., by buying time to prepare healthcare providers and the public before the arrival of the epidemic, to plan and coordinate social distancing measures, and to purchase additional pharmaceuticals such as antiviral drugs or vaccines) (38). Once an epidemic has started, travel restrictions might also be used to delay the peak of the epidemic in an isolated location where heavy seeding by incoming infected persons could accelerate local transmission. International Health Regulations could play a role in decisions on whether to implement certain international measures (39).

We identified several knowledge gaps that could be filled by further research. Most fundamentally, information is still lacking on some aspects of the basic epidemiology of influenza, including the dynamics of person-to-person transmission (e.g., Can a person be infectious before the onset of symptoms? Can transmission occur from an asymptomatic or

pauci-symptomatic case-patient? What fraction of infections are asymptomatic?). In terms of specific research on the effectiveness of travel-related NPIs, it is difficult to envisage how intervention studies could be done, but epidemiologic studies could be planned in advance of influenza pandemics or perhaps severe influenza epidemics. Studies could answer questions such as how many infections are imported from overseas or whether travel advisories might encourage infected persons not to travel.

Our review needs to be interpreted in light of some limitations. First, although international travel or trade of infected animals might have a role in the international spread of influenza, the study that assessed the movement restriction of animals was not included in this review. Second, mathematical models are useful tools for investigating the advantages and disadvantages of different interventions, but the results often depend on key modeling assumptions that are difficult to verify (19). The assessment of the quality of evidence was considered weak overall, given that most of the epidemiologic studies included in our review were ecologic studies. Third, only a few studies on the ethical and economic considerations regarding travel-related measures during influenza epidemics and pandemics were available (26,40).

Many countries continue to update their influenza pandemic plans on the basis of the latest available evidence. We found that international travel-related NPIs could delay the introduction of influenza and delay the start of local transmission; however, limited evidence exists to inform the use of these NPIs for controlling pandemic influenza. The evidence that we identified in our review does not support entry screening as an efficient or effective measure, and travel restrictions and border closures are likely to be too disruptive to consider. Additional prospective research on the effectiveness of travel-related NPIs would be valuable to support evidence-based decisions for future influenza pandemics.

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About the Author

Dr. Ryu is an assistant professor of preventive medicine at Konyang University, Daejeon, South Korea. His research interests include infectious disease epidemiology, with a focus on influenza and public health interventions.

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Address for correspondence: Benjamin J. Cowling, WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 1/F Patrick Manson Building (North Wing), 7 Sassoon Rd, Hong Kong, China; email: bcowling@hku.hk

Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—International Travel–Related Measures

Appendix

1. Screening travelers

1.1 Terminology

Screening travelers for influenza is to reduce the number of infectious individuals entering or leaving a country. Screening measures include health declarations, visual inspection, and thermography to detect individuals with influenza-related symptoms (1). These measures can be conducted at arrival terminal (entry screening) or at departure terminal (exit screening) (2).

1.2 Search strategy

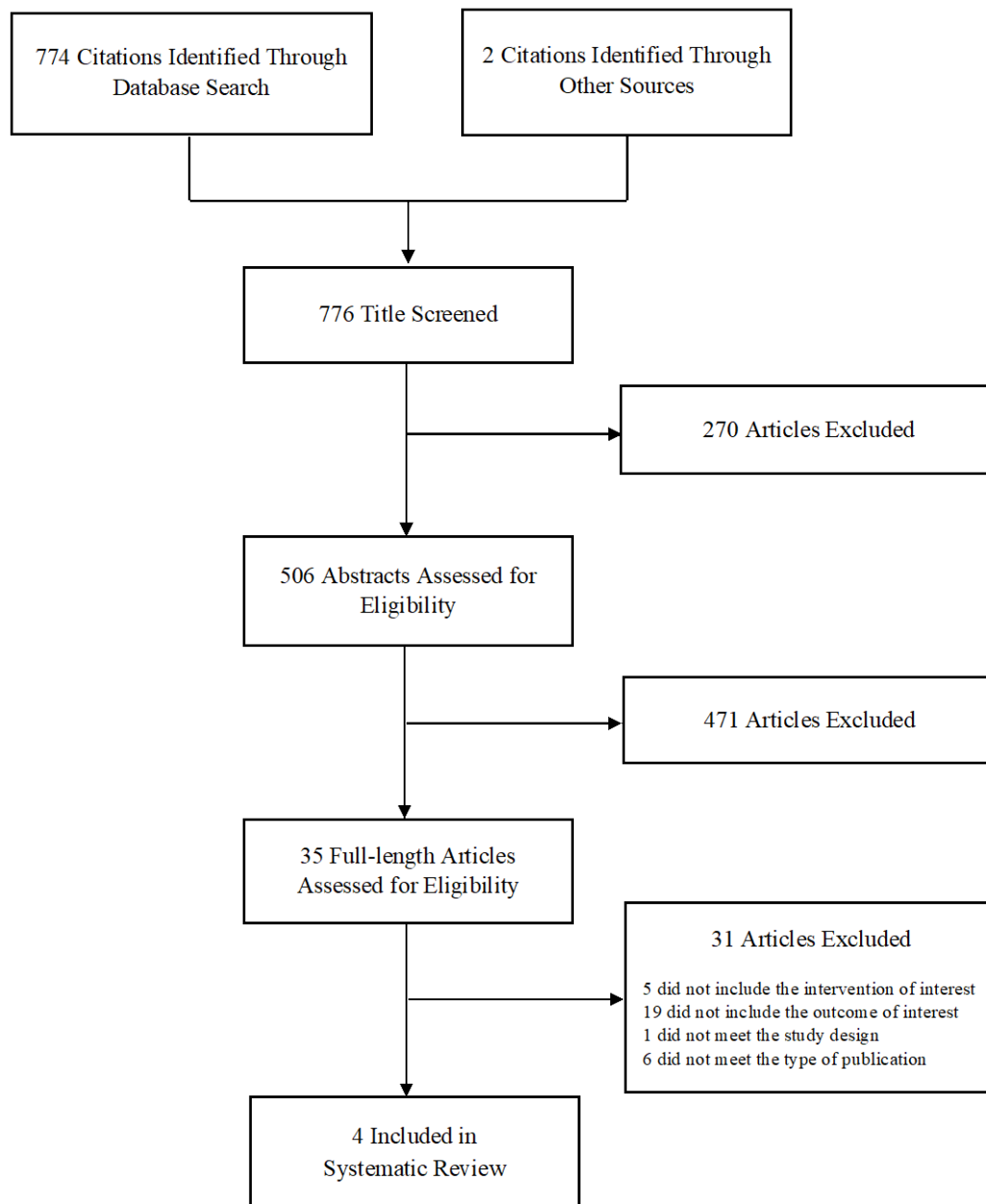
The databases including PubMed, Medline, EMBASE and Cochrane Library were searched using search terms from 1946 to 28 April 2019. Inclusion criteria were primary research evaluating entry and/or exit screening for influenza in the community setting. Studies had to demonstrate any effectiveness following entry and/or exit screening in the community. We excluded studies conducting at the healthcare settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidences, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and HG) contributed to the title, abstract, and full-text screening (Appendix Table 1).

Appendix Table 1. Search strategy for screening travelers

| Search terms | Search date | Reviewers |
|--|---------------|-----------|
| #1. travel or traveler or travelers or traveller or travelers | 29 April 2019 | SR |
| #2. screen or screening or entry screening or exit screening or entry-exit screening or massive screening or boarder screening or detect or detecting or detection | | HG |
| #3. influenza or flu | | |
| #4. #1 and #2 and #3 | | |

1.3 Findings

776 records were identified and included in the title and abstract screening, and 741 were excluded. 35 full-texts were evaluated for eligibility and 31 full-texts were excluded. Four full-length articles were included in this systematic review. Flowchart of study selection shown in Appendix Figure 1 and study details are shown in Appendix Table 2.



Appendix Figure 1. Flowchart of literature search and study selection for screening travelers.

Appendix Table 2. Summary of studies included in the review of screening travelers

| Screening travelers | Study setting | Specific measures (Location and methods) | Timing of implementation | Study results by effective indicators |
|----------------------------|--|--|---|--|
| Caley, et al. (2007) (3) | <ul style="list-style-type: none"> Simulation of a new influenza pandemic ($R_0 = 1.5, 2.5, \text{ and } 3.5$) has emerged and 400 travelers per day tried to depart from the source region where population is 5 million. | <ul style="list-style-type: none"> Entry and/or exit screening with 100% sensitivity for identifying cases presenting symptom including rhinorrhea, nasal congestion, sore throat, cough, fever and sense of fever. | <ul style="list-style-type: none"> Beginning of influenza pandemic | <ul style="list-style-type: none"> The expected median additional delay at-risk country occurred 20 infected cases was increased from 57 to 60 d ($R_0 = 1.5$ with 400 travelers per a day). However, there was no delay of reaching 20 cases ($R_0 = 3.5$ with 400 travelers per a day). |
| Cowling, et al. (2010) (4) | <ul style="list-style-type: none"> Overall, 35 countries where entry screening policies conducted during 2009 influenza pandemic were reviewed using the official report including first confirmed imported infected case and the first confirmed local infected case or untraceable case. | <ul style="list-style-type: none"> Entry screening including medical check before disembarkation, health declaration forms, symptom screening, and thermal scanners. | <ul style="list-style-type: none"> Not available | <ul style="list-style-type: none"> The entry screening policy was associated with mean additional delay of case importation (7–12 d, 95% CI: 0–30days) |
| Malone, et al. (2009) (5) | <ul style="list-style-type: none"> A stochastic discrete simulation of pandemic influenza at U.S. airport entry screening with $R_0 = 2.4$ from Europe, 2.1 from Latin America, and 2.0 from Canada and U.S.. 50% or 100% infected passengers were screened with <50% or 80% sensitivity of screening. | <ul style="list-style-type: none"> Entry screening to detect symptomatic travelers | <ul style="list-style-type: none"> Not available | <ul style="list-style-type: none"> Delay the importation of the peak of infected cases (21–1555 d) |
| Yu, et al. (2012) (6) | <ul style="list-style-type: none"> Case-based surveillance with investigation of cases linked to international travel and entry screening at the Chinese border were conducted during Influenza H1N1 pandemic in 2009, China. | <ul style="list-style-type: none"> Entry screening to detect travelers presenting symptoms | <ul style="list-style-type: none"> Early of influenza pandemic | <ul style="list-style-type: none"> Epidemic is likely delayed by 4 d in China with 37% of infected international travelers identified from the entry screening at the border. |

2. International travel restriction

2.1 Terminology

Because the airports, land transportation and maritime transportation are associated with long-distance spread of influenza (7), travel restrictions are considered as a measure to reduce regional and international spread (8). International travel restriction is to prevent the travel between particular countries (9).

2.2 Search strategy

We conducted a search using a search terms in the databases, including PubMed, Medline, EMBASE and Cochrane Library, from 1946 to 28 April 2019. Inclusion criteria were primary

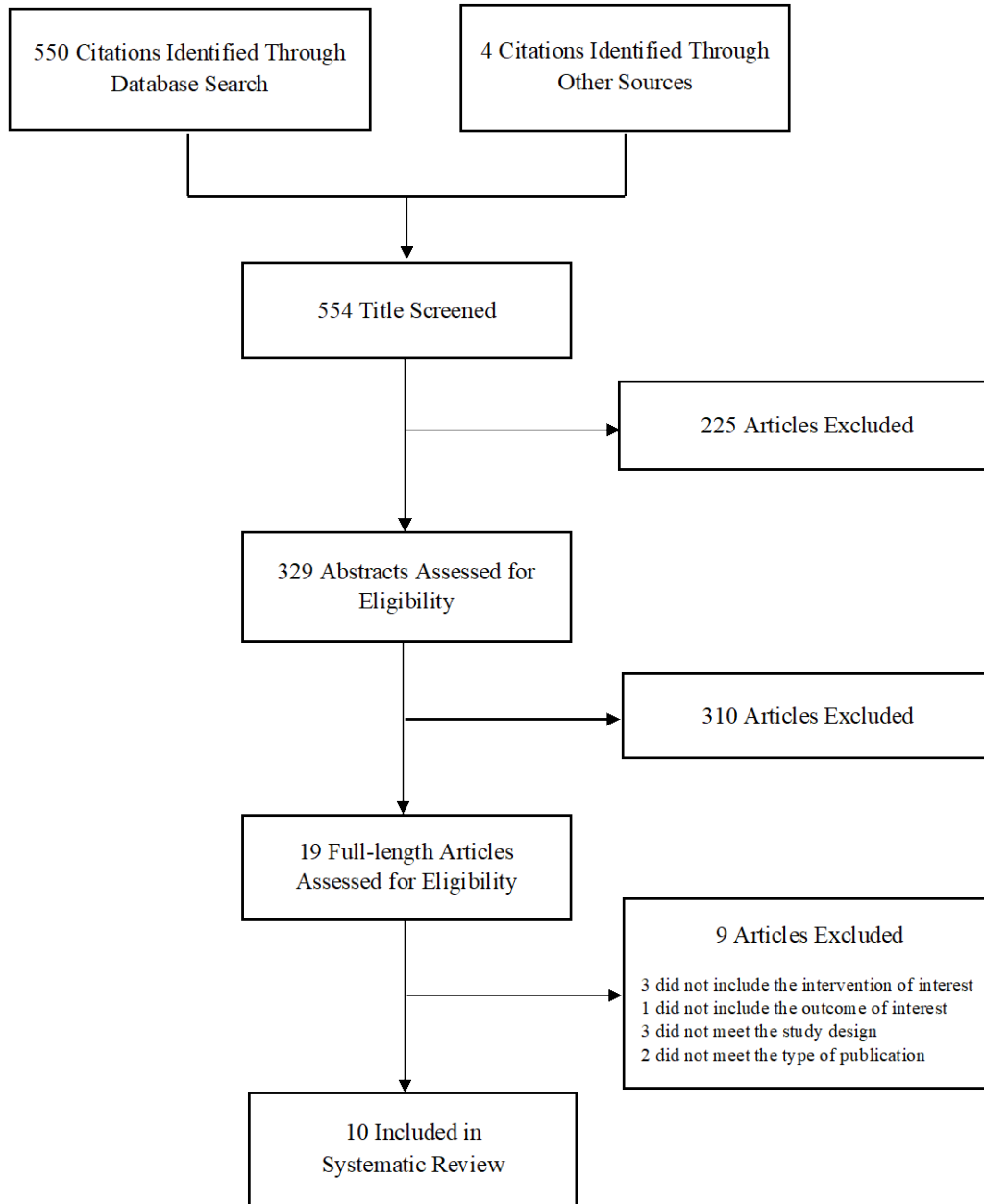
research evaluating international travel restriction for influenza endemic or pandemic in the community setting. Studies had to demonstrate any effectiveness following international travel restriction to the influenza transmission. We excluded studies conducting at the healthcare settings, animal-related studies, systematic reviews and/or meta-analysis without using primary data, not measuring effectiveness of travel restriction to the community, and article type of letter, commentary or news without primary data. Two reviewers (SR and HG) contributed to the title, abstract, and full-text screening (Appendix Table 3).

Appendix Table 3. Search strategy for international travel restriction

| Search terms | Search date | Reviewers |
|--|---------------|-----------|
| #1. travel or traveler or travelers or traveller or traveliers | 29 April 2019 | SR |
| #2. international or abroad | | HG |
| #3. restrict or restriction or prohibit or prohibition or limit or limitation or control | | |
| #4. influenza or flu | | |
| #5. #1 and #2 and #3 and #4 | | |

2.3 Findings

554 records were identified and included in the title and abstract screening, and 535 were excluded. Nineteen full-text were evaluated for eligibility and 9 of full-text were excluded. Ten full-length articles were included in this systematic review. The flowchart of study selection is shown in Appendix Figure 2 and the summary of studies is shown in Appendix Table 4.



Appendix Figure 2. Flowchart of literature search and study selection for international travel restriction.

Appendix Table 4. Summary of studies included in the review of international travel restriction

| International travel restriction | Study setting | Specific measures (Location and methods) | Timing of implementation | Study results by effective indicators |
|--------------------------------------|---|---|--|---|
| Ciofi degli Atti, et al. (2008) (10) | • Global deterministic SEIR model of pandemic influenza ($R_0 = 1.4, 1.7, \text{ or } 2.0$) in Italy was conducted. | • Incoming international flight restriction (90 or 99%) | • Thirty days after the first global case occurred | • International air travel restriction may delay the interval between first global case and the importation of the first cases by 7–37 d. • The pandemic peak may delay by 6–39 d. |
| Bajardi, et al. (2011) (11) | • SEIR-like Global Epidemic and Mobility model of using | • 40 or 90% international travel | • Early stage of the outbreak | • Estimated mean delay of the arrival of infection in influenza- |

| International travel restriction | Study setting | Specific measures (Location and methods) | Timing of implementation | Study results by effective indicators |
|----------------------------------|---|--|--|--|
| | H1N1 Pandemic influenza data 2009 ($R_0 = 1.7$ with generation interval set 3.6 d) | restriction to and from Mexico | | unaffected countries was less than 3 d (40% restriction), and ≈ 2 weeks (90% restriction). |
| Brownstein, et al. (2006) (12) | <ul style="list-style-type: none"> Seasonal influenza in U.S. $R_0 =$ Not available Time series analysis Weekly influenza mortality for nine influenza seasons (from 1996–1997 to 2004–2005) | <ul style="list-style-type: none"> International flight volume decreased by 27% | <ul style="list-style-type: none"> Since September 11, 2001 | <ul style="list-style-type: none"> The peak of influenza mortality was delayed by 2 weeks. |
| Chong, et al. (2012) (13) | <ul style="list-style-type: none"> Stochastic SEIR model of Influenza H1N1 pdm ($R_0 = 1.4$) in Hong Kong was conducted. The interval between the day of first infected cases passage and 100 infected cases passage time at the border was measured by different level and mode of border travel restriction and compared with no restriction | <ul style="list-style-type: none"> 90, or 99% travel restriction between Hong Kong and mainland China on different modes of transportation including air, land, and sea | <ul style="list-style-type: none"> On the day following the first global case identified | <ul style="list-style-type: none"> A 99% international air travel restriction may delay the interval between the first imported case and one hundred infected case passed the border by a week and the epidemic peak delayed by two weeks. A 99% international travel restriction of both air and land travel may delay the interval (passage time) by an additional one to two weeks, and the epidemic peak may be delayed ≈ 3.5 weeks. A 99% restriction of all modes of transportation may delay the interval by an additional 2 mo, and delay the epidemic peak time by ≈ 12 weeks. |
| Cooper, et al. (2006) (14) | <ul style="list-style-type: none"> Metapopulation model of SEIR ($R_0 = 1.8–5$) in Hong Kong, London, Sydney | <ul style="list-style-type: none"> 50, 90, 99, or 99.9% international air travel restriction from affected cities with susceptibility of 10%, 60%, or 100%. | <ul style="list-style-type: none"> After 1000 infected cases occurred in the originating city (Hong Kong, London and Sydney) or 100 cases occurred in other cities. | <ul style="list-style-type: none"> Median epidemic peak delay can be ranged between 7 and 102 d. |
| Eichner, et al. (2009) (15) | <ul style="list-style-type: none"> Probabilistic model using a travel data from Pacific Island Countries and Territories ($R_0 = 1.5, 2.25, \text{ and } 3.0$). Using these data, expected number of infected case entering the island was calculated, and the probability that an island either suffer an epidemic or escape a pandemic was assessed. | <ul style="list-style-type: none"> 79 or 99% restriction | <ul style="list-style-type: none"> Very beginning of a pandemic until the end or the failure to prevent case-introduction | <ul style="list-style-type: none"> Among 17 pacific island countries and territories, with 99% travel restriction, six countries (with $R_0 = 1.5$) and four to five countries (with $R_0 \geq 2.25$) would be likely escape the pandemic influenza with more than 50% probability. However, with 79% travel restriction, only one country (with $R_0 = 1.5$) and no country (with $R_0 \geq 2.25$) was likely to escape the pandemic. |
| Epstein, et al. (2007) (16) | <ul style="list-style-type: none"> Stochastic global NSSEIR model of pandemic influenza ($R_0 = 1.4, 1.7, \text{ or } 2.0$) was performed. The interval was measured between the outbreaks occurring in Hong Kong, London, or Sydney and the case-passage time to U.S. | <ul style="list-style-type: none"> 90, 95, or 99% travel restriction | <ul style="list-style-type: none"> Implemented when reached threshold of 1000 cumulative infectious cases | <ul style="list-style-type: none"> First passage time may delay from 18 d to 31 d (outbreak originated from Hong Kong), from 7days to 27 d (from Sydney), and no delay (from London) with $R_0 = 1.7$. The delays are larger for smaller R_0. |
| Ferguson, et al. (2006) (17) | <ul style="list-style-type: none"> Simulation using stochastic spatially structured mathematical individual-based model of SEIR using the scenarios of pandemic influenza ($R_0 = 1.4–2.0$) in U.S. | <ul style="list-style-type: none"> 90, 99, or 99.9% restriction to U.S. | <ul style="list-style-type: none"> From 30 d of global pandemic | <ul style="list-style-type: none"> Imported infections might delay the epidemic peak of the U.S. by 1.5 (90% restriction), 3 (99%), or 6 (99.9%) weeks |

| International travel restriction | Study setting | Specific measures (Location and methods) | Timing of implementation | Study results by effective indicators |
|-----------------------------------|---|--|--|--|
| Hollingsworth, et al. (2006) (18) | <ul style="list-style-type: none"> • Simple mathematical SEIR model of an epidemic in a source country with asymptomatic cases exported to any of 100 other countries ($R_0 = 1.8$) • Assumed 100 cases per day occurred | <ul style="list-style-type: none"> • 80, 90, or 99% travel restriction | <ul style="list-style-type: none"> • On the 20th day from first case occurred | <ul style="list-style-type: none"> • The mean time delay exporting the infected case is 5.3 (80% of restriction), 11.7 (90%), and 131.7 d (99%) |
| Lam, et al. (2011) (19) | <ul style="list-style-type: none"> • Simple stochastic model on heterogeneously mixing population on the H1N1–2009 influenza pandemic in Hong Kong ($R_0 = 1.2, 1.6, \text{ or } 2.0$) • Daily average of 10 imported cases for 50 d | <ul style="list-style-type: none"> • 100% travel restriction among children | <ul style="list-style-type: none"> • After pandemic declared | <ul style="list-style-type: none"> • Children-selective travel restriction may delay an epidemic for 19–35 d ($R_0 = 1.2$), and less than 15 d ($R_0 = 1.6 \text{ and } 2.0$) |

SEIR: Susceptible, exposed, infectious, and recovered.

NSSEIR: Nonsusceptible, susceptible, exposed, infectious and recovered.

3. Border closure

3.1 Terminology

The border closure is complete prevention of movement of individuals into and out of particular country (9).

3.2 Search strategy

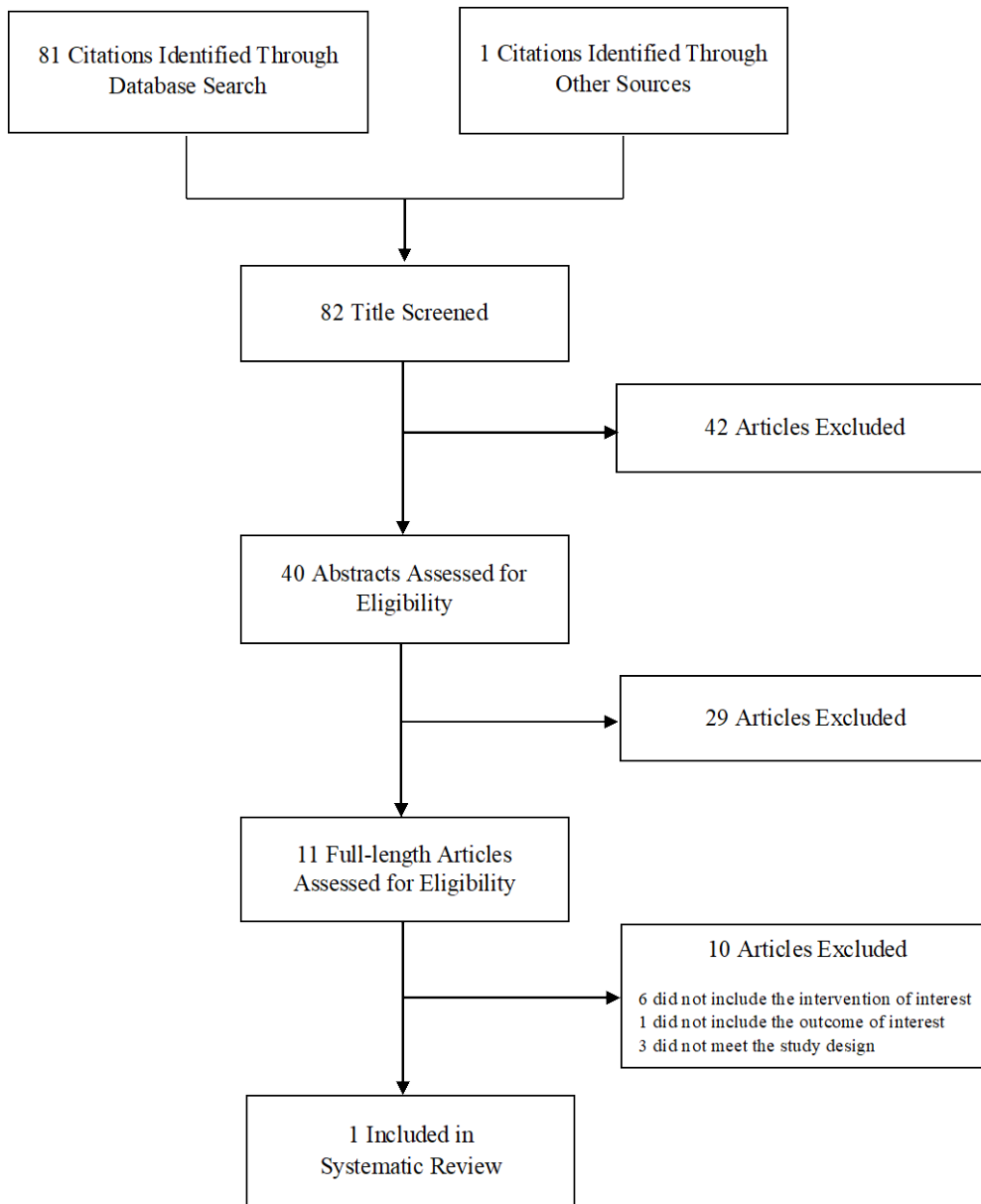
Literature searches were conducted on the databases including PubMed, Medline, EMBASE and Cochrane Library for articles published from 1946 to 28 April 2019 using search terms shown in Appendix Table 5. Inclusion criteria were primary research evaluating border closure for influenza pandemics in the community setting. Studies had to demonstrate any effectiveness following border closure in the community. We excluded studies conducted in healthcare settings, animal-related studies, systematic reviews and/or meta-analysis without primary data, not measuring effectiveness of border closure to the community, and article type of letter, commentary or news without primary data. Two reviewers (SR and HG) contributed to the title, abstract, and full-text screening (Appendix Table 5).

Appendix Table 5. Search strategy for border closure

| Search terms | Search date | Reviewers |
|---|---------------|-----------|
| #1. travel or traveler or travelers or traveller or traveliers | 29 April 2019 | SR |
| #2. border | | HG |
| #3. restrict or restriction or prohibit or prohibition or limit or limitation or control or closure | | |
| #4. influenza or flu | | |
| #5. #1 and #2 and #3 and #4 | | |

3.3 Findings

82 records were identified and included in the title and abstract screening, and 71 were excluded. Eleven full-texts were assessed for eligibility and 1 full-length articles were identified for inclusion in the systematic review. The flowchart of study selection is shown in Appendix Figure 3 and the summary of the studies shown in Appendix Table 6.



Appendix Figure 3. Flowchart of literature search and study selection for border closure.

Appendix Table 6. Summary of studies included in the review of border closure

| Border closure | Study setting | Specific measures (Location and methods) | Timing of implementation | Study results by effective indicators |
|---------------------------|---|---|--|---|
| McLeod, et al (2008) (20) | <ul style="list-style-type: none"> Reviewed mortality data and arrival of pandemic for 11 South Pacific Island jurisdictions in the 1918/1919 influenza pandemic | <ul style="list-style-type: none"> 5–7 d' maritime quarantine - American soma (5 d) - Australia, Tasmania, New Caledonia (7 d) | <ul style="list-style-type: none"> American Samoa in November 23, 1918, Australia in October 1918, and Tasmania January 27, 1919 implemented border control measures. | <ul style="list-style-type: none"> Arrival of pandemic was significantly delayed and death rates attributed to influenza per 1000 population reduced compare with the other Pacific Island Jurisdiction - American Samoa (arrival of pandemic; 1920, no death reported) - Australia (early January 1919, 2.4 death reported) - Tasmania (August 1919, 0.81 deaths reported) - New Caledonia (1921, less than 11 deaths reported) |

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