Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Social Distancing Measures

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Influenza virus infections are believed to spread mostly by close contact in the community. Social distancing measures are essential components of the public health response to influenza pandemics. The objective of these mitigation measures is to reduce transmission, thereby delaying the epidemic peak, reducing the size of the epidemic peak, and spreading cases over a longer time to relieve pressure on the healthcare system. We conducted systematic reviews of the evidence base for effectiveness of multiple mitigation measures: isolating ill persons, contact tracing, quarantining exposed persons, school closures, workplace measures/closures, and avoiding crowding. Evidence supporting the effectiveness of these measures was obtained largely from observational studies and simulation studies. Voluntary isolation at home might be a more feasible social distancing measure, and pandemic plans should consider how to facilitate this measure. More drastic social distancing measures might be reserved for severe pandemics.

Experiences from previous influenza pandemics, in particular the 2009–10 pandemic, have demonstrated that we cannot expect to contain geographically the next influenza pandemic in the location it emerges, nor can we expect to prevent international spread of infection for more than a short period. Vaccines are not expected to be available during the early stage of the next pandemic (1), and stockpiles of antiviral drugs will be limited, mostly reserved for treating more severe illnesses and for patients at higher risk for influenza complications. Therefore, nonpharmaceutical interventions (NPIs), such as social distancing (2), will be heavily relied on by health authorities to slow influenza transmission in the community, with 3 desired outcomes (Figure). The first outcome would be to delay the timing of the peak of infections

to buy time for preparations in the healthcare system, the second to reduce the size of the epidemic peak so that the healthcare system is not overwhelmed, and the third to spread infections over a longer time period, enabling better management of those cases and the potential for vaccines to be used at least later in the epidemic to reduce impact.

Influenza virus infections are believed to spread mainly through close contact in the community (e.g., homes, workplaces, preschool and day care centers, schools, public places), and more frequent and intense contact among children has a particularly major role in transmission (5). Social distancing measures aim to reduce the frequency of contact and increase physical distance between persons, thereby reducing the risks of person-to-person transmission. These measures have played a role in mitigating previous pandemics, including the 1918–19 pandemic (6,7), and are a key part of current pandemic preparedness plans (3,4). Although a clear biological and epidemiologic rationale supports the potential effectiveness of social distancing measures, there are few opportunities for rigorous controlled trials of community interventions against influenza. Our objective was to review the evidence base for social distancing measures, focusing on the evidence supporting the effectiveness of these measures in reducing influenza transmission in the community.

Methods and Results

We conducted separate systematic reviews to gather available evidence on the effectiveness of 6 measures in reducing influenza transmission in the community: isolating ill persons; contact tracing; quarantining exposed persons; school dismissals or closures; workplace measures, including workplace closures; and

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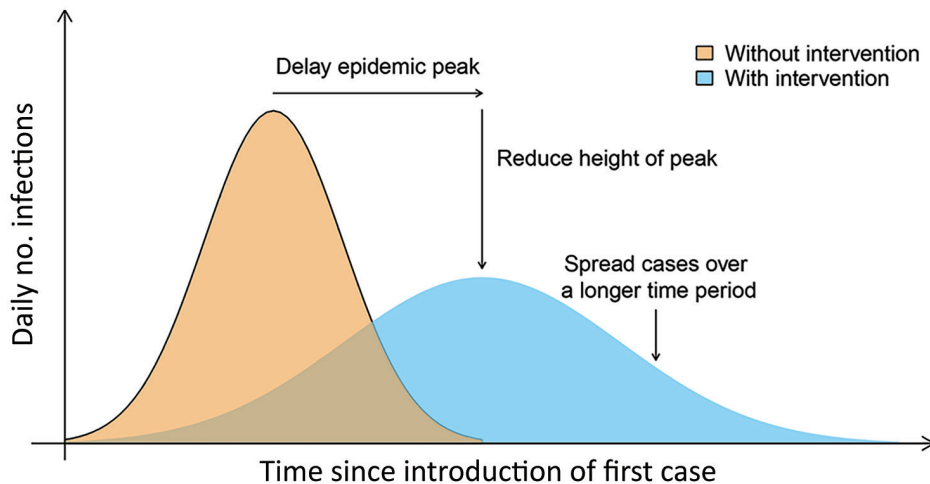
Figure. Intended impact of social distancing measures as nonpharmaceutical interventions for an influenza pandemic. Adapted from similar diagrams in the European Centre for Disease Prevention and Control Technical Report (*3*) and the Centers for Disease Control and Prevention Guidance Report (*4*).

avoiding crowding (Table 1). We retrieved literature from the Cochrane Library, Embase, Medline, and PubMed. Two authors (M.W.F. and H.G.) reviewed the retrieved literature independently for inclusion and synthesis of evidence, and a third author (J.Y.W.) resolved any discrepancies. We were unable to identify randomized controlled trials for the listed social distancing measures. Therefore, we included observational studies (contemporary as well as analysis of archival data from the 1918 pandemic) and simulation studies. We gave greater weight to observational studies than to simulation studies when we inferred the effectiveness of each measure, because assumptions and parameters in simulation studies are more difficult to assess and validate.

Isolating Ill Persons

We focused on the measure of isolating ill persons at home, but not in medical facilities, because it is unlikely that medical facilities would have the capacity for isolating persons with mild symptoms beyond the early stages of the next pandemic. We reviewed 4 observational studies (*6,8–10*) and 11 simulation studies (Appendix Tables 3, 4, https://wwwnc.cdc.gov/EID/article/26/5/19-0995-App1.pdf). Outbreaks of influenza A(H1N1)pdm09 during 2009 in various settings, including a navy ship from Peru and a physical training camp in China, have provided evidence that isolating case-patients, together with other personal protective, social distancing, and environmental measures, had substantial effect on reducing attack rates of outbreaks (*8,10*). During the 1918–19 pandemic, excess death rates caused by pneumonia and influenza decreased in some cities in the United States after a mixture of interventions were implemented, including isolation or quarantine, school closure, banning of public gatherings, and staggered business hours (*6*).

Although simulation studies were conducted on the basis of a wide range of assumptions, most of these studies suggested that isolation would reduce transmission, including reducing the epidemic size and delaying the epidemic peak. However, Fraser et al. (*11*) discussed the difficulty in controlling influenza transmission, even with high level of isolation combined with contact tracing and quarantine, because of the potentially high proportion of influenza transmission that occurs from mild or asymptomatic infections.

Given that influenza is believed to spread from person to person mostly through close contact, there is a clear rationale for preventing contact between infectious and susceptible persons. However, we found limited scientific evidence to support the effectiveness of this intervention in the community. The observational studies included in this review were conducted in atypical settings, and the effectiveness of isolation in these settings might not be generalizable to the community-at-large. Nonetheless, with the rationale discussed, and assuming that a high level of compliance with home isolation is possible for symptomatic persons, voluntary home isolation could be a preferable strategy to prevent onward transmission compared with other personal protective measures, which have not shown effectiveness in multiple randomized controlled trials.

One area in which there is a lack of evidence is the duration of infectivity, which has implications for the period of voluntary isolation. Current recommendations include voluntary isolation until cessation of fever or until 5–7 days after illness onset (*4,12*). The second recommendation would be a better trigger for uncomplicated cases without concurrent conditions, benchmarking the duration of viral shedding (*13*). Another area of uncertainty is the

Table 1. Summary of results for systematic review of literature on nonpharmaceutical interventions for pandemic influenza*

Type of NPI	No. studies identified	Study designs included	Main findings
Isolation	15	Observational, simulation	Isolation has moderate impact in reducing influenza transmission and impact.
Quarantine	16	Intervention study, observational, simulation	Quarantine has in general moderate impact in reducing influenza transmission and impact.
Contact tracing	4	Simulation	Combination of contact tracing with other measures (e.g., isolation and quarantine) can reduce influenza transmission and impact; the addition of contact tracing to existing measures might provide only modest benefit but will need substantial resources.
School closure			
Planned holiday	28	Observational	The transmission of influenza decreases during routine school holidays but might increase after schools reopen.
Reactive closures	16	Observational	The effectiveness of reactive school closure varies.
Preemptive closures	13	Observational	Preemptive school closure has moderate impact in reducing influenza transmission.
Workplace measures	18	Intervention study, observational, simulation	Workplace measures are effective; combination with other interventions will further strengthen the effect.
Workplace closures	10	Simulation	Workplace closures might have modest impact in reducing influenza transmission.
Avoiding crowding	3	Observational	Timely and sustained application of measures to avoid crowding might reduce influenza transmission.

*Details of literature review are described in the Appendix (https://wwwnc.cdc.gov/EID/article/26/5/19-0995-App1.pdf)

degree to which transmission occurs before illness onset (presymptomatic transmission) and the degree to which mild or asymptomatic cases are infectious. If there is a substantial fraction of asymptomatic transmission (14), this fraction would reduce the impact of isolation.

Contact Tracing

We reviewed 4 simulation studies, all of which found contact tracing to be effective when used in combination with other interventions, including isolation, quarantine, and prophylactic treatment with antiviral drugs (11,15–17). However, Wu et al. (15) estimated that the addition of contact tracing to an existing combination of quarantine, isolation, and antiviral prophylaxis measures would only provide modest benefit, while increasing considerably the proportion of population in quarantine and the consequent costs.

Contact tracing requires substantial resources to sustain after the early phases of a pandemic because the number of case-patients and contacts grows exponentially within a short generation time. Therefore, there is no obvious rationale for the routine use of contact tracing in the general population for control of pandemic influenza. However, contact tracing might be implemented for other purposes, such as identification of case-patients in high-risk groups to enable early treatment. There are some specific circumstances in which contact tracing might be more feasible and justified, such as to enable short delay of widespread transmission in small, isolated communities, or within aircraft settings to prevent importation of cases.

Quarantine of Exposed Persons

We reviewed 1 intervention study (18), 5 observational studies (6,19–22), and 10 simulation studies (Appendix Tables 9, 10). Miyaki et al. (18) conducted an intervention study in Japan during 2009–2010 involving 2 companies. One company was used as a control; in the other company, a change was introduced in which employees could voluntarily stay at home on receiving full pay when a household member showed development of influenza-like illness (ILI) until days after the symptoms subside. The authors reported a significant reduced rate of infections among members of the intervention cluster (18). However, when comparing persons who had an ill household member in the 2 clusters, significantly more infections were reported in the intervention group, suggesting that quarantine might increase risk for infection among quarantined persons (18).

Among the observational studies, Li et al. (20) estimated that the mandatory quarantine policy in Beijing during the influenza A(H1N1)pdm09 pandemic reduced the number of cases at the peak of the epidemic by a factor of 5 compared with a projected scenario without the intervention, and also delayed the epidemic peak, albeit at high economic and social costs (20). Similar to the intervention study in Japan, van Gemert et al. (21) reported an increased risk for infection among household contacts who were concurrently quarantined with an isolated person and estimated that the risk for infection increased with a longer duration of quarantine. The evidence base from simulation studies supplemented these

findings, and in general, quarantine is suggested to be able to reduce transmission.

In addition, we found some observational evidence for maritime and onboard quarantine. McLeod et al. (*22*) analyzed archival data for the 1918–19 pandemic from the South Pacific jurisdictions and found that strict maritime quarantine delayed or prevented arrival of the pandemic, indirectly reducing the mortality rate compared with that for islands that practiced partial or no maritime quarantine. However, the applicability of these findings is uncertain because maritime travel is uncommon in the 21st century. Conversely, Fujita et al. (*19*) reviewed the onboard quarantine experience at Narita International Airport in Tokyo, Japan, during the influenza A(H1N1) pdm09 pandemic, and reported that the intervention detected few cases and was ineffective in preventing virus entry into the country (*19*).

Overall, we found that the evidence base was weak for home quarantine. In general, the intervention is estimated to be effective. However, being able to identify case-patients and their close contacts in a timely manner can be challenging during the early phase of a pandemic, and impossible for health authorities after the early phase. Quarantine also raises major ethical concerns regarding freedom of movement because the evidence on the effectiveness is limited, providing no solid rationale for the intervention, in addition to restricting movement of some uninfected and noninfectious persons. The increased risks of infection among quarantined persons (*18,21,23*) further exacerbate the ethical concerns. Therefore, voluntary/self-quarantine is likely to be preferred over mandatory quarantine in most scenarios (*24*). No evidence-based insights or discussions have addressed the optimal duration of quarantine or deactivating trigger. Theoretically, a quarantine duration of 4 days might be sufficient, covering 2 incubation periods of influenza (*25*). If necessary, the duration could be adjusted once the incubation period distribution of the pandemic virus strain is established. Prolonged quarantine can cause substantial burden to social services and working persons (*26*). Some measures can be taken to minimize the possible harms, such as pairing quarantine with antiviral prophylaxis provision for the household (*23*).

School Dismissals or Closures

School dismissal refers to the situation where a school campus remains open with administrative staff and teachers present but most children stay at home. Schools can then continue to provide meals for children from low-income families or look after children of essential workers. School closure is a stricter intervention in which a school campus is closed to all children and all staff. Although most of the currently available studies on the impact of school dismissals or closures on influenza transmission are presented as studies of school closures, we found that the interventions applied were in some instances school dismissals. Because it was not always possible to identify whether a scenario involved closure or dismissal, and because we expected the effects of closure and dismissal on transmission to be roughly similar, we did not distinguish between the 2 scenarios in our systematic review.

Jackson et al. (*27*) published a systematic review in 2013 that included 79 epidemiologic studies on school closures and found compelling evidence that school closures could reduce influenza transmission, especially among school-age children. However, the duration and the optimal timing of closure were not clear because of the heterogeneity in the available data, and transmission tended to increase when schools reopened (*27*). To update the evidence base presented by Jackson et al., we identified 22 additional studies published since 2013 and included 101 epidemiologic studies in total (Appendix Tables 14–17). Most of these studies were conducted in primary and secondary schools; only a few studies were conducted in universities. Overall, findings from the updated systematic review supported the conclusions by Jackson et al.

Thirteen studies investigated preemptive school closures, in which schools are closed with the aim of slowing transmission in the community (*28*). A correlation analysis between weekly mortality rates and interventions (which included school closure) during the 1918–19 pandemic in cities in the United States estimated that early and sustained interventions reduced mortality rates by <25% (*29*). Two studies conducted in Hong Kong as a public health response to influenza A(H1N1)pdm09 estimated that school closures, followed by planned school holidays, reduced influenza transmission (*30,31*).

We found 16 studies reporting the effectiveness of reactive school closures, in which individual schools or groups of schools were closed after substantial ILI outbreaks in those schools (*28*). Two studies conducted in Japan estimated that the peak number of cases and the cumulative number of cases were reduced by ≈24% (*32*) and 20% (*33*). However, some studies estimated that reactive school closures had no effect in reducing the total attack rate and duration of school outbreaks, and the spread of influenza (*34–36*).

The effect of routine school holidays in reducing influenza transmission was investigated in 28 studies. Planned school holidays were estimated to reduce influenza transmission and delay the time to epidemic peak occurrence for >1 week (37,38). In some instances, transmission resurged after schools reopened (39).

It is well established that school children play a major role in spreading influenza virus because of higher person-to-person contact rates, higher susceptibility to infection, and greater infectiousness than adults (40,41). Therefore, school closures or dismissals are a common-sense intervention to suppress transmission in the community, and several observational studies have confirmed that overall transmission of influenza in the community is reduced when schools are closed. However, major caveats are noted in the literature, primarily that transmission will only be reduced when schools are closed. In some past epidemics, closing of schools after the epidemic peak showed little impact on the overall attack rate and none on the timing of the peak or the size of the epidemic peak because it has already passed (27). In other past epidemics, transmission resurges after schools reopen, so that the closures delayed the epidemic peak but might not necessarily have reduced the size of the epidemic peak or the overall attack rate (27). Although these points seem obvious, the appropriate timing and duration of school closures can be difficult to discern in the heat of an epidemic with delays in information and difficulties in interpreting surveillance data.

School closures can also have adverse impacts on ethical and social equity, particularly among vulnerable groups (e.g., low-income families), which could be ameliorated by dismissing classes, but allowing some children to attend school for free school meals or to enable parents to go to work. Extended school closures might increase domestic travel and contact rates in households and other social gatherings (e.g., malls, theaters), with the potential to increase transmission in the community. The optimum combination of timing, geographic scale, and duration of school closure might differ for the control of different epidemic/pandemic scenarios (42). A useful area for further research would be providing validated tools to enable real-time estimation of not only how an epidemic or pandemic is progressing (43), but also what the public health impact of an intervention, such as school closure, would be with alternative choices of timing and duration.

Workplace Measures and Closures

Workplace measures and closures aim to reduce influenza transmission in workplaces or during the commute to and from work. Teleworking at home, staggered shifts, and extended holidays are some common workplace measures considered for mitigating influenza pandemics. A systematic review of workplace measures by Ahmed et al. (2) concluded that there was evidence, albeit weak, to indicate that these measures could slow transmission, reduce overall attack rates or peak attack rates, and delay the epidemic peak. We updated the evidence base with 3 additional recently published studies and obtained similar results (Appendix Table 20). Paid sick leave could improve compliance with a recommendation to stay away from work while ill (44,45).

We conducted a separate search for evidence on the effectiveness of workplace closures in influenza pandemics and identified 10 studies, all of which were simulation studies (Appendix Table 21). In general, the simulation studies predicted that workplace closures would be able to reduce transmission somewhat in the community, but probably would have a smaller effect on transmission than school closures.

We found limited evidence that workplace measures and closures would be effective in reducing influenza transmission. Two recent studies not included in our systematic review have contrasting findings on the effect of having paid sick leave and taking a day off from work because of ILI (46,47). As with school closures, the timing and duration of workplace interventions would be a critical issue affecting their impact in mitigating a pandemic. This scenario is an area with rich potential for intervention studies to contribute higher quality evidence (e.g., teleworking policies or staggered shifts). However, workplace measures and closures could have considerable economic consequences, and inclusion in pandemic plans would need careful deliberations over which workplaces might be suitable for application of interventions, whether to compensate employees or companies for any loss in income or productivity, and how to avoid social inequities in lower income workers, including persons working on an ad hoc basis.

Avoiding Crowding

We reviewed 3 observational studies (6,48,49). Timely bans on public gatherings and closure of public places, including theaters and churches, were suggested to have had a positive effect on reducing the excess death rate during the 1918 pandemic in the United States (6,48). During an influenza outbreak that occurred during World Youth Day 2008, a higher attack rate was reported among a group of pilgrims accommodated in 1 large hall than in pilgrims sleeping in smaller groups (49).

The evidence for avoiding crowding is limited. The implementation of measures to avoid crowding

might require a large amount of resources (e.g., financial and trained personnel), which might be less feasible in low-income and middle-income countries. Measures to avoid crowding might also be difficult to implement in some settings because of cultural and religious reasons (e.g., Hajj).

Discussion

Overall, our systematic reviews suggested that social distancing measures could be effective interventions to reduce transmission and mitigate the impact of an influenza pandemic. However, the evidence base for these measures was derived largely from observational studies and simulation studies; thus, the overall quality of evidence is relatively low. Natural experiments or controlled studies of single or combined interventions are needed to clarify the use of social distancing measures; improve knowledge on basic transmission dynamics of influenza, including the role of presymptomatic contagiousness and the fraction of infections that are asymptomatic (50); determine the optimal timing and duration for implementation of these measures, and school closures in particular; and provide cost-benefit assessment for implementation of these measures (Table 2).

Table 2. Knowledge gaps on social distancing measures as nonpharmaceutical interventions for pandemic influenza and suggested areas for future study

Intervention	Knowledge gaps	Suggested studies
Isolation of sick persons	Few observational studies use laboratory-confirmed influenza as outcome and study isolation as a single intervention; most observational studies were in atypical settings; transmission dynamics of influenza: role of presymptomatic contagiousness, fraction of infections that are asymptomatic, duration of infectivity; optimal strategy for symptomatic persons, trigger to stop isolation	Randomized trials in community settings to evaluate the effectiveness of voluntary isolation against transmission of laboratory-confirmed influenza; epidemiologic studies to understand transmission dynamics of influenza, including symptomatic profiles and duration of infectiousness; compliance of the public with voluntary isolation at home
Contact tracing	Value of adding contact tracing on top of other existing interventions remain unclear; strategy for feasible implementation	Might not be a research priority for pandemic preparedness because of the lack of feasibility of this intervention
Quarantine of exposed persons	Few observational studies use laboratory-confirmed influenza as outcome and provide evidence on the effect of quarantine as a single intervention or the value quarantine adds to existing interventions; transmission dynamics of influenza: fraction of infections that are asymptomatic, possibility of superspreaders; optimal duration of quarantine	Randomized trials in community settings to evaluate the effectiveness of quarantine against transmission of laboratory-confirmed influenza; epidemiologic studies to understand transmission dynamics of influenza including the incubation period and the asymptomatic fraction
School closures	Triggers to close and reopen schools; optimal timing and duration of school closures, taking into account the possible disruptions to the public; compliance of persons of different socioeconomic status; alternative school-based measures, such as staggering lunch breaks and increasing spacing between desks: feasibility and effectiveness	Observational studies on optimal closure triggers and duration, taking into account the possible disruptions brought by school closures; comprehensive review of the acceptance and compliance of the interventions by different subgroups of the population; develop tools to enable real-time estimation of epidemic or pandemic growth, and the effect of implementing closures at different time points of the epidemic/pandemic; while school-based measures were not specifically covered in our systematic review, it would be useful to examine randomized trials of measures to prevent influenza transmission in schools, such as increasing spacing between desks during influenza seasons
Workplace measures and closures	Triggers to close and reopen workplaces; optimal timing and duration of workplace closure, taking into account the possible disruption to the public; alternative workplace measures (e.g., improving teleworking infrastructure, or providing segregated working areas for persons with mild symptoms): feasibility and effectiveness, cost-benefit	Randomized control trials to evaluate the effectiveness of workplace measures (e.g., telework from home, staggered shifts, weekend extension and paid-leave policies) against laboratory-confirmed influenza transmission; studies on optimal triggers, timing and duration for workplace measures and closures, taking into account the possible disruptions caused by workplace measures; cost-benefit analyses of alternative workplace measures
Avoiding crowding	Methods to reduce population density in different settings (e.g., transport hub, mass events, and public places): feasibility and effectiveness	More observational or simulation studies on the alternative methods to avoid crowding in different settings.
Combined interventions	Limited evidence on synergy of alternative interventions or the best combinations of interventions	Policy studies to identify feasible interventions that would complement each other when combined

Although we reviewed the evidence for each NPI individually, it is common for social distancing measures to be implemented in combination. For example, during the 1918 pandemic, multiple NPIs were implemented simultaneously in some cities in the United States, including school closures and public gathering bans (*6*). Although simulation studies have estimated progressively increasing effectiveness as more NPIs are added, we believe that some thought should be given to identifying interventions that would complement each other when combined. Social distancing measures such as school closures and mall closures could be implemented simultaneously to prevent an increase in social contact rates outside schools. School closures could also be paired with teleworking policies to provide opportunities for parents to take care of school-age children at home.

Despite the limitations and uncertainties, social distancing measures will be useful components of the public health response to the next pandemic. Careful consideration of these measures is required when composing pandemic plans, particularly in terms of public compliance and resource planning and distribution. Recommending that ill persons stay at home is probably the most straightforward social distancing measure, and pandemic plans should consider how to enable ill children and employees to stay at home from school or work. For example, health authorities might recommend suspending the usual requirement for doctors' notes to support absence from school or work. Finally, although our review focused on nonpharmaceutical measures to be taken during influenza pandemics, the findings could also apply to severe seasonal influenza epidemics.

In conclusion, our review found some evidence from observational and simulation studies to support the effectiveness of social distancing measures during influenza pandemics. Timely implementation and high compliance in the community would be useful factors for the success of these interventions. Additional research on transmission dynamics, and research on the optimal timing and duration of school and workplace closures would be useful.

About the Author

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EMERGING INFECTIOUS DISEASES **October 2018**

Influenza

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Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Social Distancing Measures

Appendix

Isolation of Sick Persons

Terminology

Terms relevant to isolation are defined below (Appendix Table 1):

Appendix Table 1. Definition of terms relevant to isolation

Term	Definition
Isolation	"Separation or restriction of movement of ill persons with an infectious disease to prevent transmission to others" (*1*).
Case isolation	"Separation or restriction of movement of ill persons with an infectious disease" at home or in a healthcare facility to prevent transmission to others (*1,2*).
Patient isolation	Isolation of ill persons with an infectious disease in a healthcare facility to prevent transmission to others (*2*).
Home isolation	Home confinement of ill persons with an infectious disease (often not needing hospitalization) to prevent transmission to others (*1,2*).
Voluntary isolation	Voluntary "separation or restriction of movement of ill persons" in a designated room to prevent transmission to others. This is usually in their own homes, but could be elsewhere (*1*).
Self-isolation	Refer to 'Voluntary isolation'

Search Strategy

Literature search was conducted using PubMed, MEDLINE, EMBASE, and CENTRAL to identify literature that were available from 1946 through August 4, 2018. No language limit was applied for the literature search, however literatures in languages other than English were excluded during full-text screening. The inclusion criteria is studies reporting the effectiveness of isolation on control of influenza in nonhealthcare settings. No limitation on study design was applied for study inclusion because preliminary works have identified no randomized-controlled trial for this topic. Systematic review and metaanalyses, as well as studies involving clinical settings were excluded. Two reviewers (M.W.F. and H.G.) independently screened the titles, abstracts and full-texts to identify articles for inclusion (Appendix Table 2).

Appendix Table 2. Search strategy for isolation

Search terms	Search date	Reviewers
#1: "patient isolation" OR "case isolation" OR "voluntary isolation" OR "home isolation" OR "social isolation" OR "self-isolation" #2: "influenza" OR "flu" #3: #1 AND #2	5 August 2018	M.W.F., H.G.

Findings

The initial database search yielded 588 articles, of which 70 were selected for full-text screening based on their title and abstract contents. Of these, 56 articles were excluded; main reasons for exclusion of relevant articles include absence of discussion on effectiveness of isolation and focus on healthcare setting. One other study for inclusion was identified through snowball searches. The study selection process is detailed in Appendix Figure 1.

Of the 15 included studies, 4 are epidemiologic studies, comprising of an analysis of historical data from the 1918–1919 pandemic in 43 cities in the United States and 3 outbreak investigations which occurred in an elderly home in France, a training camp in China, and on a Peruvian navy ship respectively (Appendix Table 3) (*3–6*). The remaining 11 are simulation studies (Appendix Table 4 (*7–16*). Isolation was implemented in the outbreaks as a combination with various other interventions such as antiviral prophylaxis and use of a face mask. Isolation was also studied as a single intervention or combined with other interventions in the 11 simulation studies. It is of note that the simulation studies were conducted based on a wide range of assumptions, for example asymptomatic fraction and contact rate reduction brought forth by isolation, hence providing wide-ranging insights on effectiveness of isolation in different scenarios. These included studies focused mostly on reduction of attack rate, epidemic size, transmissibility, and delay in epidemic peak as outcomes-of-interest. All but one study suggested favorable impact of isolation, or combination of isolation with other interventions.

Reduction of Impact

Eight studies suggested decrease in attack rate (AR) brought about by implementation of case isolation (*3,6–8,10–12,14*). An individual-based simulation model for Great Britain and the United States suggested rapid isolation could reduce the cumulative clinical attack rate from 34% to 27% for a pandemic with R_0 2.0, assuming uniform reductions in contact rates in schools, workplaces and households (*7*). Kelso et al. reported similar findings, in which case isolation alone is able to prevent an epidemic (<10% infected) in a 30,000 persons community with R_0 1.5, when 90% of cases are isolated and such measure is implemented within 3 weeks from the introduction of an initial case (*11*). Although isolation alone has been suggested to be more impactful than other interventions, combination with other interventions further improved the effectiveness (*10–12,14*). In addition, increase in isolation rate is quasi-linearly correlated with decrease in attack rate of influenza (*8*).

A reduction in the cumulative incidence of infections due to an isolation policy was also recorded during an influenza A(H1N1)pdm09 outbreak on a navy ship (*6*). A combination of isolating cases of influenza-like illness (ILI), use of masks and hand sanitizers was implemented. The clinical attack rate in the outbreak was 23.9%, a significant reduction from the 97% projected in the absence of any intervention. This also corresponded to a reduction in the effective reproduction number (R) from 1.55 to 0.7 with the intervention. Chu et al. reported similar findings in an outbreak in a physical training camp, in which the final AR recorded was ≈25% of the projected AR of 81% in absence of previous exposure, immunity, and any interventions. In the 1918–19 pandemic, excess death rates due to pneumonia and influenza decreased in New York City and Denver after isolation and quarantine were implemented (*5*).

Conversely, Fraser et al. discussed the difficulty in controlling influenza even with high level of case isolation combined with contact tracing and quarantine, due to the high proportion of asymptomatic transmission of influenza (*9*). The probability of self-isolation without increased public health effort by persons in the community have also been suggested to be high, at 50% and 90% for adult and children respectively (*11*).

Delay of Epidemic Peak

The study of Flauhault et al. suggested that case isolation would have the strongest impact on global spread of a pandemic involving 52 cities compared with air travel restrictions and antiviral treatment, such that isolation of 40% of cases would delay the epidemic by 83 days compared with absence of any intervention (*8*). A combination of isolation of 10% of symptomatic cases with 60% reduction in air traffic on the other hand would delay the start of epidemics in each city by an average of 19 days with considerable case reduction (*8*). The study of Wang et al. study showed similar effect albeit focusing on arrival time of influenza pandemic, in which isolation of a moderate proportion of cases delayed the arrival of the pandemic in a subpopulation for about a month, in the circumstance of high compliance and early implementation (*13*). Delay in response will reduce the effectiveness. Combined intervention with quarantine, school closure, community contact reduction, and personal protective measures further augmented the effect (*12*).

Reduction in Transmissibility

Zhang et al. showed in their simulation studies that isolation of cases can reduce household reproduction number to below one, and compensate delay in antiviral drug distribution by 1 to 2 days. Compliance for isolation has to be much higher to offset longer delays (*15*,*16*). An

outbreak in an elderly home in France reported an abrupt cessation of outbreak after case isolation, antiviral treatment and prophylaxis were implemented (*4*). Reduction in reproduction number was also recorded in the navy ship outbreak previously described, by 54% from 1.55 to 0.7 with a combination of interventions (*6*). The projected reproduction number without isolation of cases was 4.5.
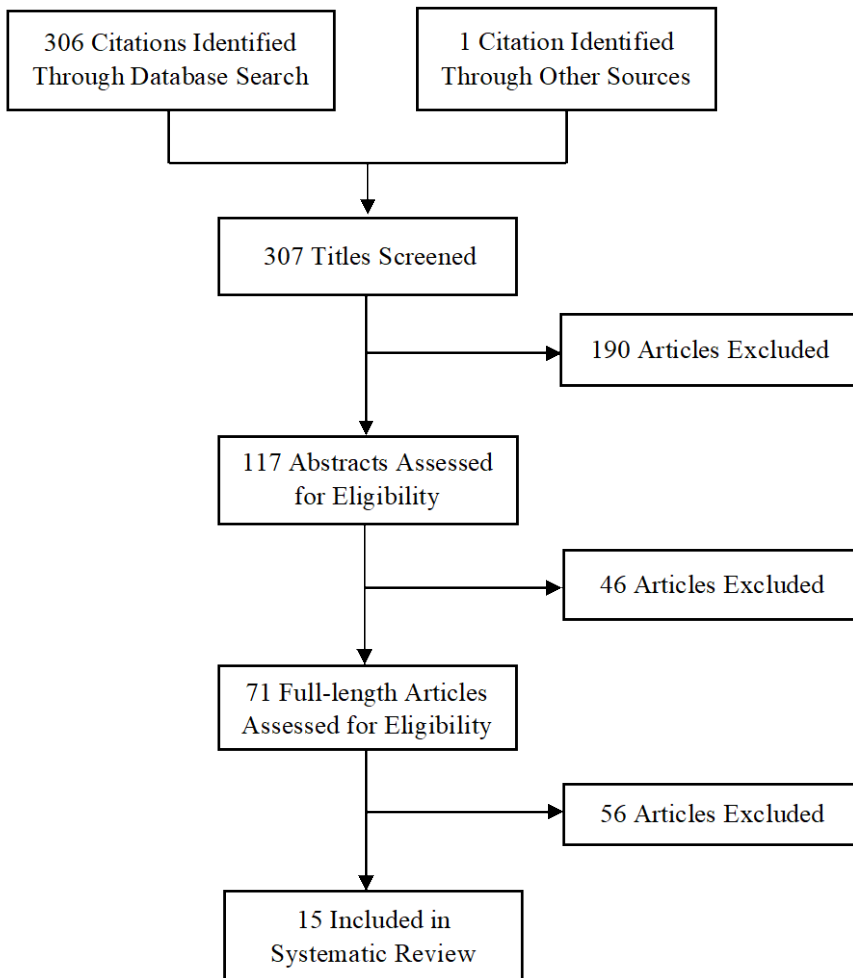
Appendix Figure 1. Flowchart of literature search and study selection for isolation.

Appendix Table 3. Summary of epidemiologic studies included in the review of isolation

Author, year published	Influenza strain or transmissibility (R_0)	Type of study	Study setting and population	Intervention	Comparison	Results and findings
Chu C, 2017 (*3*)	A(H1N1)pdm09	Outbreak investigation	Outbreak in a physical training camp in China with 3256 persons	Combination of isolation with other interventions including oseltamivir treatment and prophylaxis, face-mask usage, cancellation of training and group activities, ventilation and disinfection (implemented within a few days of surge in ILI)	Projected scenario (without previous exposure, immunity and any interventions)	(1) 72.7% clinical cases were reported before intervention, 27.3% after intervention (2) The clinical attack rate recorded for the outbreak was 18.2%, while the projected attack rate in absence of previous exposure, immunity and any interventions was 80.9%
Gaillat J, 2008 (*4*)	Seasonal	Outbreak investigation	Outbreak in elderly home with 81 residents in summer (recorded attack rate of 39.5%)	Sick residents were immediately isolated and used face-masks, oseltamivir treatment and prophylaxis were given to residents and staffs	Not available	No new case was reported among residents and staffs within 2 d of implementation of intervention
Markel H, 2007 (*5*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the United States; used historical mortality rate data from the US Census Bureau and other historical archival documents	Combination of school closure, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	Cities with different timing, duration and combination of non-pharmaceutical interventions	(1) All 43 cities implemented at least one intervention, 15 cities implemented all three interventions. Cities that started implementation earlier had lower peak mortality and total mortality rates (2). Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when school closure, isolation and quarantine were implemented
Vera DM, 2014 (*6*)	A(H1N1)pdm09	Outbreak investigation, stochastic model	Outbreak on a navy ship with 355 crews	Suspected ILI cases were placed in isolation, active case-finding, face mask and hand hygiene, and antiviral provision	Projected scenario (without isolation)	(1) Significant reduction in reproduction number during implementation of interventions (54.4%, from 1.55 to 0.7). The projected reproduction number without isolation was 4.5. (2) Clinical attack rate recorded was 23.9%, while the projected rate was 97%.

Appendix Table 4. Summary of simulation studies included in the review of isolation

Author, year published	Transmissibility of influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
Flahault A, 2006 (*8*)	3.1 in tropical zone, 0.3–3.4 in other geographic locations due to seasonal variations	(1) Global spread of influenza pandemic from Hong Kong to 52 cities by air trave; (2) Pre-existing immunity in a quarter of the population, 60% of cases are symptomatic	(1) Combination of isolation (10% of symptomatic persons excluded from simulation model) and 60% air traffic reduction (implemented since day 1). (2) Combination of (*1*) with antiviral treatment and vaccination	No intervention	(1) Isolation cause reduction in number of cases by 9%; (2) Cities took on average 19 more days to attain epidemic status when a combination of isolation and air traffic reduction is implemented; (3) Epidemic is delayed by on average 83 d with 40% of case isolation; number of cases ecreased by 65% with a combination of isolation, air traffic reduction, antiviral provision, and vaccination

Author, year published	Transmissibility of influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
Fraser C, 2004 (*9*)	Upper bound of R_0 was 21	(1) Early stage of disease outbreak in a community with homogenous mixing (2) Proportion of pre-symptomatic transmission is 30%–50%	Isolation of symptomatic persons contact-tracing and quarantine of some persons who were infected before symptomatic persons were isolated; Interventions were implemented without delay. Efficacy of isolation considered were 75%, 90%, and 100%; contact tracing and isolation were assumed to be fully effective.	Not available	Control of influenza is challenging even at high level (90%) of quarantine and contact tracing, due to the considerable proportion of pre-symptomatic transmission.
Halloran ME, 2008 (*10*)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million persons) with variations in the population structure; (2) 67% infections are symptomatic, case ascertainment levels are 60%–80%	Combination of home isolation (compliance 60/90%; assumed intrahousehold contacts not affected) with quarantine and other social distancing measures, implemented at intervention thresholds of 1, 0.1, and 0.01%	No intervention	At R_0 of 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, the attack rate was 0.17%–1.2%, compared with baseline scenario of 42.4%–46.8%
Kelso JK, 2009 (*11*)	1.5, 2.5, and 3.5	(1) Population of 30,000 with contacts in schools, workplaces, other facilities, and between neighboring persons; (2) Asymptomatic fraction mimics that of seasonal influenza	(1) Isolation (assumed no contact outside household, adults and children are 90% and fully compliant respectively; (2) Combination of isolation with school closure, staying away from work and general reduction in community contact	No intervention	(1) An epidemic (≥10% attack rate) at R_0 of 1.5 can only be prevented by case isolation introduced within 3 weeks (as a single intervention), daily attack rate can also decrease from 90/10,000 to <35 if isolation is implemented within a month; (2) Attack rate decreased from 33% to 9% when all 4 measures were implemented together, influenza control is more difficult at higher R_0
Saunders-hastings P, 2017 (*12*)	1.5–2.5	(1) Model based on the population structure of Ottawa–Gatineau census metropolitan area in 2011	Combination of isolation with other interventions including vaccination, antiviral treatment and prophylaxis, school closure, reduction in community contact, personal protective measures, and quarantine; best estimate for compliance for voluntary isolation is 30%	No intervention	(1) Attack rate reduced to 33.9% from the baseline of 53.4% when a combination of isolation and quarantine was implemented, such combination was the most effective among all other interventions studied; (2) Attack rate further reduced to 15.2% and pandemic peak was delayed to more than 100 d when combination of isolation, quarantine, school closure, reduction in community contact and personal protective measures
Zhang Q, 2015 (*16*)	2.5	(1) A community with household distribution based on the Australian census data in 2001; (2) Most infection occur within households and community transmission is negligible	Self-isolation (assumed intra-household contacts remain the same), or combination with antiviral prophylaxis	No intervention	Self-isolation can decrease household reproduction number, compensating the negative impacts of delay in antiviral provision of 1 and 2 d. The compliance for self-isolation have to be considerably higher to compensate for 2 d delay
Zhang Q, 2014 (*15*)	1.5	(1) Stable population with homogenous mixing(2) Asymptomatic fraction is 0.5, and symptomatic cases are 2 times more infectious	Isolation or combination with antiviral prophylaxis	No intervention	(1) Reproduction number decreased to <1 when case isolation is implemented (2) Cumulative number of infections decreased substantially when case isolation is combined with use of antiviral prophylaxis

Author, year published	Transmissibility of influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
Ferguson NM, 2006 (7)	1.4–2.0	(1) Model based on population density and travel behavior data of the U.S. and Great Britain (2); 30% of transmission occur in household, the rest in the wider community, workplaces and schools; asymptomatic fraction was 0.5	Rapid case isolation (assumed uniform reduction of contact including household contacts)	No intervention	Cumulative attack rates decreased from the baseline of 34% to 27% for a pandemic with R_0 2.0 if 90% of cases were rapidly isolated
Wu JT, 2006 (14)	1.80	(1) Model based on population structure of Hong Kong (i.e. household sizes and average number of children in households); (2); 1.5 infected persons introduced each day per 100,000 persons for a year; (3); 70% of transmission occur outside household (e.g., in schools and workplaces)	Combination of isolation and voluntary quarantine. Interventions were active before arrival of infected persons in the city.	No intervention	Attack rate decreased from baseline of 74% to 43% when combination of isolation and voluntary quarantine is implemented.
Wang L, 2012 (13)	1.75	International spread of influenza to cities during the early phase of a pandemic	Isolation (assumed isolated persons have little chance to cause infection, isolation was implemented by removing some infectious persons from the model)	No intervention	Isolation of a moderate proportion of cases delayed the arrival of the pandemic for about a month, in the circumstance where cases were fully compliant and intervention was started at the first instance of the pandemic
Yasuda H, 2009 (17)	A(H1N1)pdm09	Community of 8,800 persons with family structures based on Japanese census data	Home isolation of 1/3 adults and 70%–100% of school-aged children	No intervention	Home isolation of 1/3 adults and all children decreased one-third of the total number of infection

Contact Tracing

Terminology

Contact tracing is the identification and follow-up of persons who may have come into contact with an infected person (*18*). Although contact tracing is often coupled with quarantine or provision of antiviral prophylaxis to exposed contacts, the term contact tracing does not involve these processes.

Search strategy

A literature search was conducted by using PubMed, MEDLINE, EMBASE, and CENTRAL to identify literature available from 1946 to 11 November 2018. No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. The inclusion criteria were studies reporting the effectiveness of contact tracing on the control of influenza in nonhealthcare settings. No limitation on study design was applied for study inclusion because preliminary works have identified no RCTs for this topic. Systematic reviews and metaanalyses, as well as studies involving clinical settings were excluded. Two reviewers (M.F. and S.G.) independently screened the titles, abstracts and full texts to identify articles for inclusion (Appendix Table 5).

Appendix Table 5. Search strategy for contact tracing

Search terms	Search date	Reviewers
#1: "contact tracing" OR "trace contact" OR "trace contacts" OR "identify contact" OR "identify contacts" OR "case detection" OR "detect cases" OR "case finding" OR "find cases" OR "early detection" #2: "influenza" OR "flu" #3: #1 AND #2	12 November 2018	M.W.F., H.G.

Findings

The initial database search yielded 1188 articles, of which 75 were selected for full-text screening based on their title and abstract contents. Of these, 71 articles were excluded; the main reasons for exclusion of these articles include absence of discussion on effectiveness of contact tracing and irrelevance. The study selection process is detailed in Appendix Figure 2.

All 4 studies were simulation studies (*9,14,19,20*). None studied contact tracing as a single intervention; instead, this measure was studied in combination with other interventions, such as quarantine, and isolation and provision of antiviral drugs (Appendix Table 6). Such combinations of interventions have been suggested to reduce transmission and delay the epidemic peak (*9,14,20*).

Reduction of Impact

Wu et al. estimated in their simulation model of an influenza pandemic with a reproductive number (R_0) of 1.8 that the combination of contact tracing, quarantine, isolation and antivirals can reduce the infection attack rate from the baseline of 74% to 34% (*14*). However, the addition of contact tracing on top of quarantine and isolation measures was suggested to provide only modest benefit, while at the same time greatly increasing the proportion of quarantined persons. Conversely, Fraser et al. suggested that it would be difficult to control influenza even with 90% contact tracing and quarantine, due to the high level of presymptomatic or asymptomatic transmission in influenza (*9*).

Delay of Epidemic Peak

In an epidemic of R_0 1.58 in the population structure of Germany, a combination of isolation, treatment of cases, contact tracing, quarantine and postexposure prophylaxis for both community and household contacts, in addition to some household-focused measures, have been estimated to delay the epidemic peak for up to 6 weeks, assuming a case detection rate of 10%– 30% (*20*). The authors assumed that the above combination of measures would be 75% effective in reducing secondary cases, and household-focused measures would be 50% effective.

Reduction in Transmissibility

Peak et al. compared the combination of contact tracing with quarantine or symptom monitoring in the early phase of an epidemic with an R_0 of 1.54 (*19*). The study suggested that contact tracing combined with quarantine was more effective than a combination with symptom monitoring in reducing transmission.
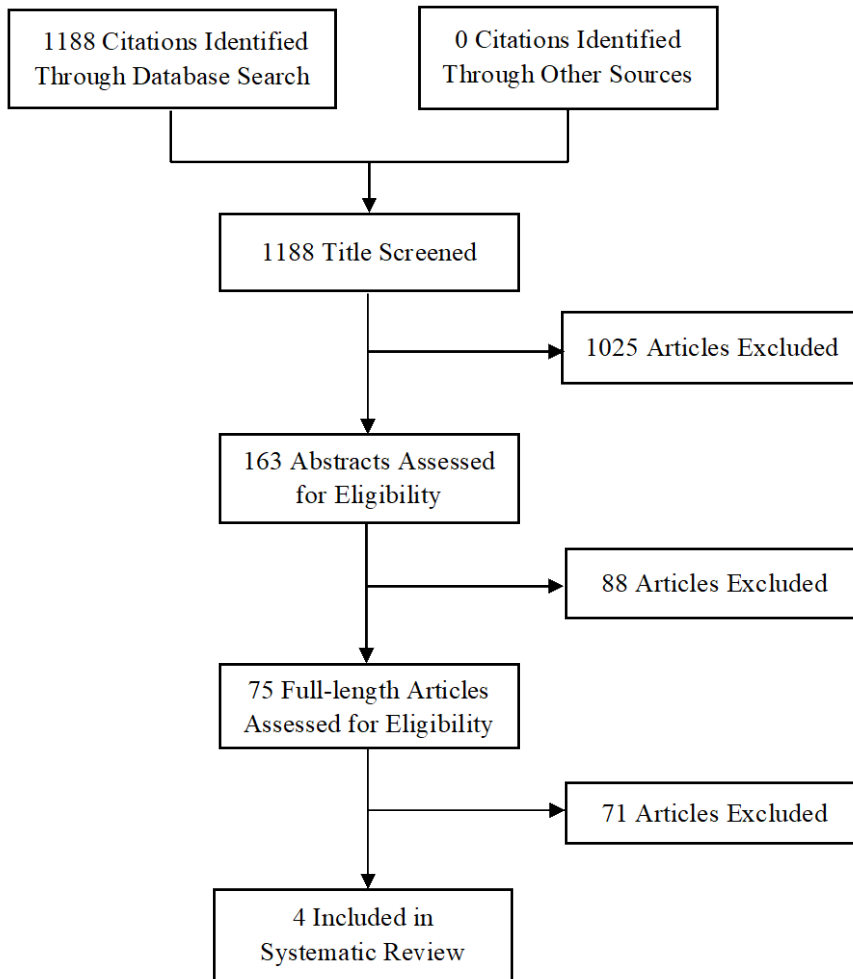
Appendix Figure 2. Flowchart of literature search and study selection for contact tracing

Appendix Table 6. Summary of studies included in the review of contact tracing

Author, year published	Transmissibility of the influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
Wu JT, 2006 (*14*)	1.80	(1) Model based on population structure of Hong Kong (i.e., household sizes and average number of children in households) (*2*); 1.5 infected persons introduced each day per 100,000 persons for a year (*3*); 70% of transmission occur outside household (e.g., in schools and workplaces)	Combination of contact tracing with other interventions such as quarantine, isolation and antivirals. For contact tracing, persons were asked to name on average five members of their peer group. The contacts of all new symptomatic or hospitalized cases were traced with a mean delay of 1 d. Contacts were asked to take precautionary measures. Interventions were active before arrival of infected persons in the city	No intervention	Attack rate decreased from baseline of 74% to 40% when combination of isolation, quarantine and antivirals is implemented. Addition of contact tracing to the combination of interventions further reduced attack rate to 34%, but increased considerably the proportion of population in quarantine
Peak CM, 2017 (*19*)	1.54	(1) Initial infected population of 1000 persons during the early phase of an epidemic (*2*); no substantial depletion of susceptibles within first few generations of transmission	Symptomatic contacts were isolated immediately, asymptomatic contacts were placed under quarantine (in a high performance scenario, delay in contact tracing was 0.5 ± 0.5 d, 90% of contacts were traced, 50% of traced contacts were infected)	Asymptomatic contacts were placed under symptom monitoring instead of quarantine	Combination of contact tracing with quarantine is more effective in reducing reproduction number compared with combination of contact tracing with symptom monitoring
Fraser C, 2004 (*9*)	Upper bound of R_0 was 21	(1) Early stage of disease outbreak in a community with homogenous mixing (2) Proportion of pre-symptomatic transmission is 30%–50%	Isolation of symptomatic persons, contact-tracing and quarantine of some persons who were infected before symptomatic persons isolated; Interventions were implemented without delay. Efficacy of isolation considered were 75%, 90%, and 100%; contact tracing and isolation were assumed to be fully effective.	Not available	Control of influenza is challenging even at high level (90%) of quarantine and contact tracing, due to the considerable proportion of pre-symptomatic transmission.
an der Heiden M, 2009 (*20*)	1.34, 1.58, 2.04	(1) Model based on the population structure of Germany: 71,000,000 adult and 11,000,000 children (<15 y old), whole population is completely susceptible at the beginning of the epidemic (*2*); Children are 2.06 times more susceptible than adults, 86% of infected persons show development of symptoms	(1) Intensive case-based measures (CCM1; consisting of isolation and treatment of cases, contact tracing, quarantine and post-exposure prophylaxis of some household and community contacts) (*2*); Less-intensive measures (CCM2; isolation and treatment of cases, quarantine and post-exposure prophylaxis of only household contacts); CCM1 and CCM2 were assumed to be 75% and 50% respectively in their effectiveness to reduce secondary cases	No intervention	(1) When the initial 500 cases were subjected to CCM1 and the subsequent 10,000 cases CCM2, the peak of the epidemic is delayed for up to 6 weeks (R_0 1.58, 5 imported cases per day, case detection rate 10%–30%). If only CCM1 was adopted, the delay was estimated to be 6–20 d (case detection rate 10%–30%) (*2*); Effectiveness of these combination of interventions is affected by the R_0 of the influenza strain and case detection rate, i.e., higher R_0 causes interventions to be ineffective at an earlier time point.

Quarantine of Exposed Persons

Terminology

Terms relevant to quarantine are defined below (Appendix Table 7):

Appendix Table 7. Definition of terms relevant to quarantine

Term	Definition
Quarantine	Imposed "separation or restriction of movement" of persons who are "exposed, who may or may not be infected but are not ill," and "may become infectious to others" (1).
Household quarantine	Confinement (commonly at home) of non-ill household contacts of a person with proven or suspected influenza (1,2).
Home quarantine	Home confinement of non-ill contacts of a person with proven or suspected influenza.
Self-quarantine	Voluntary confinement of non-ill contacts of a person with proven or suspected influenza.
Work quarantine	1) Measures taken by workers "who have been exposed and who work in a setting where the disease is especially liable to transmit (or where there are people at higher risk from infection), e.g. people working in elderly homes and nurses in high risk units" (1). 2) Measures taken by healthcare workers who "chose to stay away from their families when off-duty so as not to carry the infection home" (1).
Maritime quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a ship is permitted in a jurisdiction (21).
Onboard quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a flight is permitted (22). Also known as 'airport quarantine' (22).

Search Strategy

A literature search was conducted by using PubMed, MEDLINE, EMBASE, and CENTRAL to identify literature that were available from 1946 through July 23, 2018. Similar to isolation, no limitation on language and study design were applied for the literature search. Literatures in languages other than English were excluded during full-text screening. Studies reporting the effectiveness of quarantine on control of influenza in nonhealthcare settings were included. Systematic reviews and metaanalyses, as well as studies involving clinical settings were excluded. Two reviewers (M.W.F. and H.G.) independently screened the titles, abstracts and full-texts to identify articles for inclusion (Appendix Table 8).

Appendix Table 8. Search strategy for quarantine

Search terms	Search date	Reviewers
#1: "quarantine" #2: "influenza" OR "flu" #3: #1 AND #2	24 July 2018	M.W.F., H.G.

Findings

The initial database search yielded 1873 articles, of which 120 were selected for full-text screening based on their title and abstract contents. Of these, 104 articles were excluded; the main reasons for exclusion of relevant articles include absence of discussion on effectiveness of

quarantine and focus on healthcare setting. The study selection process is detailed in Appendix Figure 3.

The included studies were comprised of 10 simulation studies (Appendix Table 10) (*7,10,12,14,20,23–27*). The epidemiologic studies included 1 modeling study based on pandemic influenza A(H1N1)pdm09 transmission in Beijing (*28*), 2 analyses of historical data (1918–19 influenza pandemic in the United States and South Pacific, respectively) (*5,21*), and 2 observational studies and an intervention study in Japan (Appendix Table 9) (*22,29,30*). Quarantine measures studied include home quarantine, household quarantine, border quarantine as well as maritime quarantine. Quarantine was studied as a single intervention or as a combination with other interventions, commonly with isolation and antiviral prophylaxis. These included studies focused mostly on reduction of attack rate, transmissibility, and delay in epidemic peak as outcomes-of-interest.
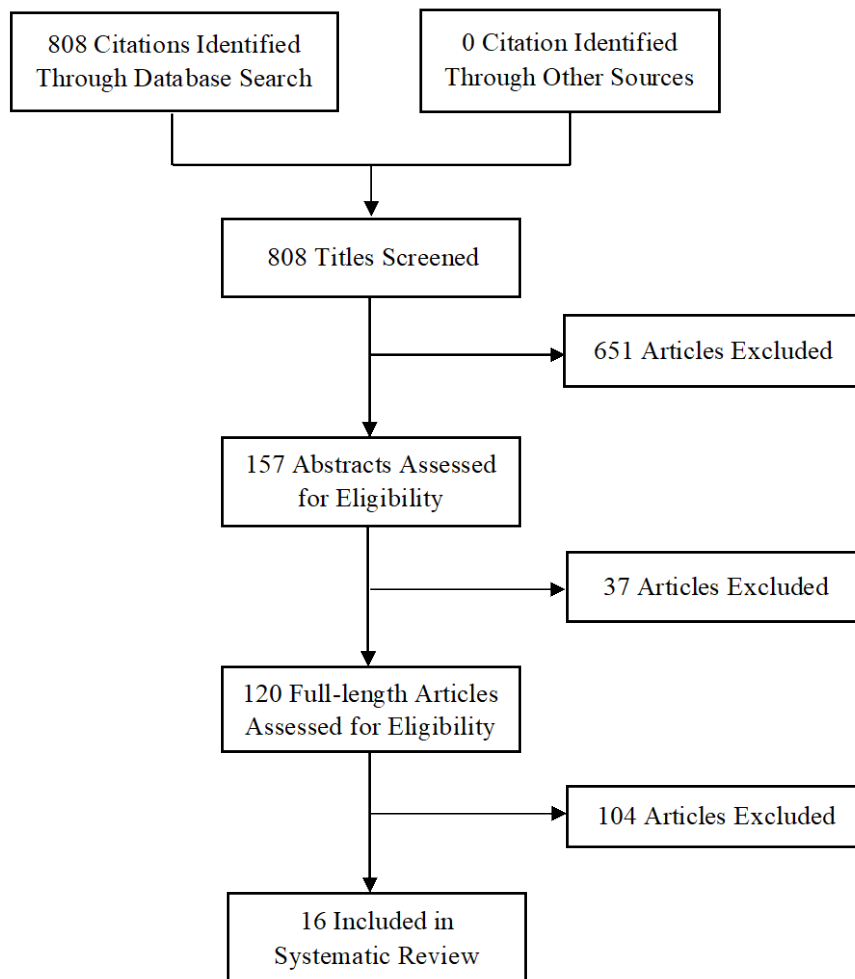
Appendix Figure 3. Flowchart of literature search and study selection for quarantine.

Five studies suggested reduction in attack rate with implementation of household quarantine measures (*7*,*10*,*12*,*14*,*29*). Miyaki et al. conducted an intervention study in Japan in 2009–2010, which involved 2 companies. Employees of 1 company were used as a control group while in the other company, employees were asked to voluntarily stay at home on full pay if a family member was experiencing ILI. The intervention reduced risk and number of infections for members of the cluster and in the workplace involved (*29*).

Ferguson et al. reported in their simulation study that household quarantine were effective in reducing attack rate at R_0 1–4.2, especially so at low values (*7*). Combination of quarantine with other interventions such as home isolation, provision of antiviral prophylaxis, school closure and workplace distancing were suggested to further reduce the cumulative incidence of infections (*7*,*10*,*14*).

Household quarantine has also been suggested to be highly effective in reducing peak and total number of cases in a pandemic, provided that compliance is high (*27*). Longini et al. reported similar findings, that is the effectiveness of household quarantine in reducing number of cases is conditioned by high compliance at 70% and relatively low R_0, in addition to early implementation (*23*). Border quarantine on the other hand has been suggested to cause minimal impact on reduction of number of cases (*26*).

Both analyses of historical data of the 1918–19 pandemic studied the effectiveness of interventions on mortality rates (*5*,*21*). When a combination of isolation and quarantine was implemented, excess death rates due to pneumonia and influenza decreased in New York City and Denver (*5*). Maritime quarantine in the pacific islands have also delayed or prevented arrival of the epidemic, indirectly reducing mortality rates in the jurisdictions (*21*).

Both household quarantine and border quarantine have been suggested to reduce transmission, albeit with moderate effectiveness (*22*,*24*,*25*). Fujita et al. assessed the onboard quarantine inspection experience in Japan during the 2009 H1N1 pandemic, and reported minimal impact in detecting and preventing entry of cases; however, following-up with passengers thereafter was found to be effective in preventing secondary infection in the community from travelers (*22*). Nishiura et al. also suggested that border quarantine of 9 days would prevent 99% of entry of infectious travelers into small island nations (*24*).

Increased Risk for Household Contacts

Although it showed a reduction of the infection rate in the intervention cluster, the intervention study of Miyaki et al. also reported that more persons became ill in the intervention group when there was an ill family member (*29*). The likelihood of a household contact (concurrently quarantined with an isolated individual) becoming a secondary case has been estimated to increase with each day of quarantine (*30*).

Appendix Table 9. Summary of epidemiologic studies included in the review of quarantine

Author, year published	Influenza strain or transmissibility (R₀)	Type of study	Study setting and population	Intervention	Comparison	Results and findings
Markel H, 2007 (*5*)	1918 pandemic H1N1	Analysis of historical data	43 large U.S. cities; used mortality records from the U.S. Census Bureau and other archival documents	Combination of school closure, public gathering bans, isolation and quarantine (both mandatory)	Cities with different timing, duration and combination of non-pharmaceutical interventions	(1) All 43 cities implemented at least one intervention, 15 cities implemented all 3 together. Cities that started implementation earlier have lower peak and total mortality rates (*2*); Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when school closure, isolation and quarantine were implemented
Fujita M, 2011 (*22*)	A(H1N1)pdm09	Observational	Japan (passengers at Narita International Airport for onboard quarantine inspection and Japan at-large for the outbreak)	Onboard quarantine inspection was conducted for over 25 d, on 500 flights carrying 120069 passengers. Cases (identified by thermography screening and positive rapid test) and persons seated around them were isolated. If cases were subsequently confirmed of their infection by PCR, cases were isolated while persons seated around them were quarantined	Not available	Onboard quarantine inspection detected few cases and was ineffective in preventing virus entry into the country. Onboard quarantine however increase the ease to trace and monitor travelers when they are in town, subsequently reduce/ prevent onward transmission in the community.
Li X, 2013 (*28*)	A(H1N1)pdm09	Model based on epidemiologic dynamics of influenza A(H1N1)pdm09	Beijing (N = 20 million); used data of daily confirmed cases reported by Beijing Municipal Bureau of Health (May-July 2009)	Mandatory quarantine for all close contacts	Projected scenario (without mandatory quarantine)	Reduced number of cases at peak of epidemic to 5 times less than the projected scenario in which mandatory quarantine was not conducted, and delayed epidemic peak. Pandemic size remained the same and authors discussed on high economic and social costs of quarantine
McLeod MA, 2008 (*21*)	1918 pandemic H1N1	Analysis of historical data	South Pacific islands (including Australia); used records from national archives of relevant countries, government departments, and international organizations	Maritime quarantine (monitoring all passengers and crew for on average 5–7 d before allowing disembarkation)	Jurisdictions with partial or no maritime quarantine implemented	Strict maritime quarantine have delayed or prevented arrival of the pandemic in said jurisdictions, and associated with reduced mortality rate. Partial quarantine (*i.e.* routine release, no quarantine of asymptomatic passengers) in Fiji and Tahiti was unsuccessful, as in other jurisdictions that did not adopt any border control interventions
Miyaki K, 2011 (*29*)	A(H1N1)pdm09	Intervention study	15,134 general employees (aged 19–72 y) of two sibling companies in japan.	Employees in the intervention cluster were asked to stay home voluntarily on full pay if any household family members showed development of ILI, until 5 d after ILI symptoms	Employees in the control cluster reported to work as usual even when a household member is experiencing ILI	Infection in workplace is significantly reduced among the intervention cluster, however participants in this group are more likely to be infected when there is an infected household member

Author, year published	Influenza strain or transmissibility (R_0)	Type of study	Study setting and population	Intervention	Comparison	Results and findings
			subside or 2 d after cessation of fever.			
van Gemert C, 2011 (*30*)	A(H1N1)pdm09	Retrospective cross-sectional	Confirmed cases reported to the Victorian Department of Health, Australia from May–June 2009 (n = 36 index case-patients, 131 household contacts)	Antiviral drug usage (treatment and prophylaxis) and household quarantine	Not available	The likelihood of a household contact (who was concurrently quarantined with a case) to become infected increase for each additional day of quarantine (adjusted OR 1.25, 95% CI 1.06–1.47)

Appendix Table 10. Summary of simulation studies included in the review of quarantine

Author, year published	Transmissibility of influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
an der Heiden M, 2009 (*20*)	1.34, 1.58, 2.04	(1) Model based on the population structure of Germany: 71,000,000 adult and 11,000,000 children (<15 y old), whole population is completely susceptible at the beginning of the epidemic (*2*); Children are 2.06 times more susceptible than adults, 86% of infected persons show development of symptoms	(1) Intensive case-based measures (CCM1; consisting of isolation and treatment of cases, contact tracing, quarantine and post-exposure prophylaxis of some household and community contacts) (*2*); Less-intensive measures (CCM2; isolation and treatment of cases, quarantine and post-exposure prophylaxis of only household contacts); CCM1 and CCM2 were assumed to be 75% and 50% respectively in their effectiveness to reduce secondary cases	No intervention	(1) When the initial 500 cases were subjected to CCM1 and the subsequent 10,000 cases CCM2, the peak of the epidemic is delayed for up to 6 weeks (R_0 1.58, 5 imported cases per day, case detection rate 10%–30%). If only CCM1 was adopted, the delay was estimated to be 6–20 d (case detection rate 10%–30%) (*2*); Effectiveness of these combination of interventions is affected by the R_0 of the influenza strain and case detection rate, i.e., higher R_0 causes interventions to be ineffective at an earlier time point.
Saunders-hastings P, 2017 (*12*)	1.5–2.5	(1) Model based on the population structure of Ottawa–Gatineau census metropolitan area in 2011	Combination of quarantine with other interventions including vaccination, antiviral treatment and prophylaxis, school closure, reduction in community contact, personal protective measures, and isolation; best estimate for compliance for quarantine is 15%	No intervention	(1) Combination of quarantine and isolation caused greatest impact in reducing the attack rate among all interventions studied. Attack rate was reduced to 33.9% from the baseline value of 53.4%. (2) Combination of quarantine, isolation, school closure, community-contact reduction and personal protective measures further decreased the attack rate to 15.2% and delayed the epidemic peak to more than hundred days
Ferguson NM, 2006 (*7*)	1.4–2.0	(1) Model based on population density and travel behavior data of the United States and Great Britain (*2*); 30% of transmission occur in household, the rest in the wider community, workplaces and schools; asymptomatic fraction was 0.5	Voluntary household quarantine for 14 d (assumed 50% compliance, contact rates outside household reduced by 75% and intra-household contact rate doubled)	No intervention	Voluntary household quarantine was effective in reducing community attack rate and delaying epidemic peak, in the circumstance of high compliance. A combination of household quarantine and antiviral prophylaxis provision could further strengthen the effect, at the same time alleviate the ethical dilemma due to the increased risk for infection among quarantined persons
Wu JT, 2006 (*14*)	1.80	(1) Model based on population structure of Hong Kong (i.e., household sizes and average	Combination of isolation and voluntary quarantine (household quarantine of on average 7.2–8.2 d). Interventions were	No intervention	Attack rate decreased from baseline of 74% to 43% when combination of isolation and voluntary quarantine is implemented.

Author, year published	Transmissibility of influenza strain (R_0)	Study setting and population	Intervention	Comparison	Results and findings
		number of children in households) (*2*); 1.5 infected persons introduced each day/100,000 persons for a year (*3*); 70% of transmission occur outside household (e.g., in schools and workplaces)	active before arrival of infected persons in the city		
Halloran ME, 2008 (*10*)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million persons) with variations in the population structure (*2*); 67% infections are symptomatic, case ascertainment levels are 60%–80%	Combination of household quarantine (for 10 d with compliance of 30%, 60% or 90%) with isolation, and other social distancing measures, implemented at intervention thresholds of 1, 0.1, and 0.01%	No intervention	At R_0 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17%–1.2%, compared with baseline scenario of 42.4%–46.8%
Sato H, 2010 (*26*)	2.3	(1)Population of 100,000 persons; (2) Cases which was not detected during onboard quarantine inspection caused transmission in the population	Onboard quarantine combined with school closure and home quarantine (with compliance of 10%, 30% and 50%; quarantined persons were assumed to have no contact with infectious persons for 3, 7, or 14 d)	No intervention	The interventions were effective in reducing maximum number of daily symptomatic cases and delaying the epidemic peak. Such effectiveness depend on compliance; low compliance result in low impact. Home quarantine for 14 d starting on day 6, with compliance of 50% was the most effective, which reduced number of cases by 44% and delayed the epidemic peak by 17 d
Longini IM Jr, 2005 (*23*)	1.4	Population of 500,000 persons with population structure based on the 2000 census in Thailand, and social network structure in rural Thailand	Household quarantine; quarantined persons were assumed to have two times more contact with their household and household cluster members	No intervention	Household quarantine alone was effective in reducing number of cases. Early implementation and high compliance is needed for successful intervention
Nishiura H, 2009 (*24*)	1.67	Small island nation with no previous case, 20 aircrafts (with 8000 passengers and crews in total) arrived in the nation before closure of all airports	All incoming passengers and crews were quarantined on arrival and monitored for symptoms. All infected persons who become symptomatic were successfully detected. Isolation and quarantine were completely effective and no secondary transmission within the facilities	No intervention	Quarantine of 9 d can decrease 99% of risks of introducing infectious persons into small island nations. Combination with rapid diagnostic testing can reduce the quarantine period to 6 d
Roberts MG, 2007 (*25*)	2.0	(1) Population of one million persons (2) 67% of infected persons show development of symptoms; asymptomatic persons have 50% infectivity when compared with symptomatic persons	(1) Home quarantine (70% compliance) for 6 d, which prevents 56% of all transmission from those infected within their household. (2) Home quarantine (50% compliance), which prevents 40% of transmission from household contacts (3) Combination of home quarantine with school closure, and targeted antiviral prophylaxis	No intervention	Home quarantine alone was effective in reducing the reproduction number, as well as the proportion of population infected. At higher transmissibility, R_0 3.0, only the combination of home quarantine with school closure and targeted antiviral prophylaxis is effective in preventing an epidemic
Yang Y, 2011 (*27*)	1.79	(1) Population of 8382 persons, with population and social structure based on the city of Eemnes	(1) Household quarantine (home confinement at all times with compliance 25%, 50%, 75%, and 100%). (2) Combination of household quarantine with school closure and avoiding social activities; Delay between interventions and outbreak threshold was less than one day	No intervention	At 50% compliance, household quarantine reduced 12.5% and 20.8% of total number of cases and peak cases respectively, as well as delayed epidemic peak. A combination of all 3 interventions did not add much benefit in reducing the total number of cases, however reduced the peak cases by 56%, and delayed the epdemic peak

School Closures

Terminology

Closure of schools include scenarios either when virus transmission is observed in the school, or an early planned closure of schools before influenza transmission initiates. Types of closure are shown in Appendix Table 11 (*31*).

Appendix Table 11. Definition of terms relevant to school closures

Term	Definition
School closure	School is closed to all children and staff.
Class dismissal	School campus remains open with administrative staff and teachers, but most children stay home.
Reactive Closure/ Dismissal	School is closed after a substantial incidence of ILI-related illnesses is reported among children and/or staffs in that school.
Pre-emptive Closure/ Dismissal	School is closed before a substantial transmission among children and staff is reported.

Search Strategy

The latest systematic review to review the effects of school closures on influenza outbreaks was published in 2013 by Jackson et al. (*32*). To update the systematic review, we conducted additional search in PubMed, Medline, EMBASE, and CENTRAL to identify literature available from January 1, 2011 through September 3, 2018. Inclusion criteria included study designs of randomized controlled trials, epidemiologic studies and modeling studies reporting the effectiveness of school closure. Studies that described ≥ 1 influenza outbreaks, as well as the combination of school closure and other nonpharmaceutical interventions (NPIs) were also included. Modeling studies were included only if they used influenza surveillance data to evaluate the effectiveness of school closure. Modeling studies based on simulated data or on avian influenza virus, studies without school-specific data, and studies published other than full report were excluded. Articles published other than English were also excluded after full-text screening. Two reviewers (H.G. and M.W.F.) independently screened titles, abstracts and full texts to identify the eligible articles (Appendix Table 12).

Appendix Table 12. Search strategy for school closures

| Search terms	Search date	Reviewers
#1: "school closure" OR "class dismissal" OR "school holiday" OR "community mitigation" OR "social distancing" #2: "influenza" OR "flu" #3: #1 AND #2	4 September 2018	H.G., M.W.F.

Findings

The most recent systematic review was published in 2013. Jackson et al. identified 79 epidemiologic studies on school closures and summarized the evidence as demonstrating that this

intervention could reduce the transmission of pandemic and seasonal influenza among school-children, but the heterogeneity in the available data illustrated that the optimum strategy (e.g., the length of closure, reactive or pre-emptive closure) remained unclear (*32*). The flowchart of study selection is shown in Appendix Figure 4.

In the additional search to update the systematic review that was published by Jackson et al. in 2013, a total of 287 papers were identified from the 4 databases, and 12 citations were found in other sources, resulting in 299 citations for screening. A total of 101 full-length articles were assessed for eligibility, and 22 additional articles were identified. A total of 101 articles were included in our systematic review. The flowchart of study selection is shown in Appendix Figure 5.

Among the included 101 articles, 16 articles had data on reactive school closures (*33–48*), 13 articles examined preemptive school closures (*5,49–60*), 28 articles examined the impact of regular school holidays on transmission (*45,47,58,61–85*), and 47 articles were related to outbreak reports or teachers' strikes (*86–132*). The basic characteristic of the studies is shown in Appendix Table 13.
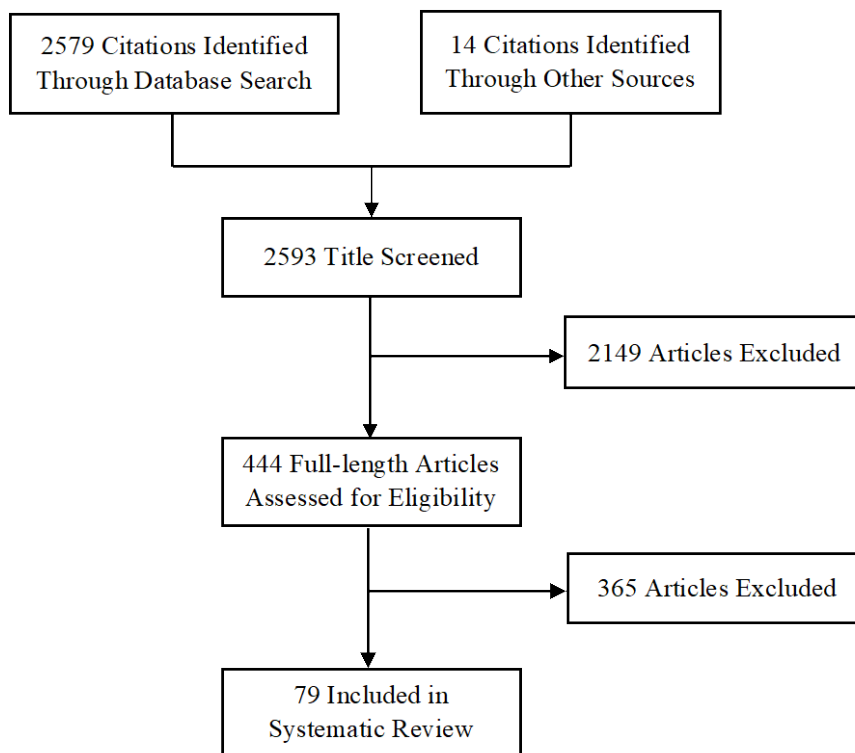
Appendix Figure 4. Flowchart of systematic review by Jackson et al.
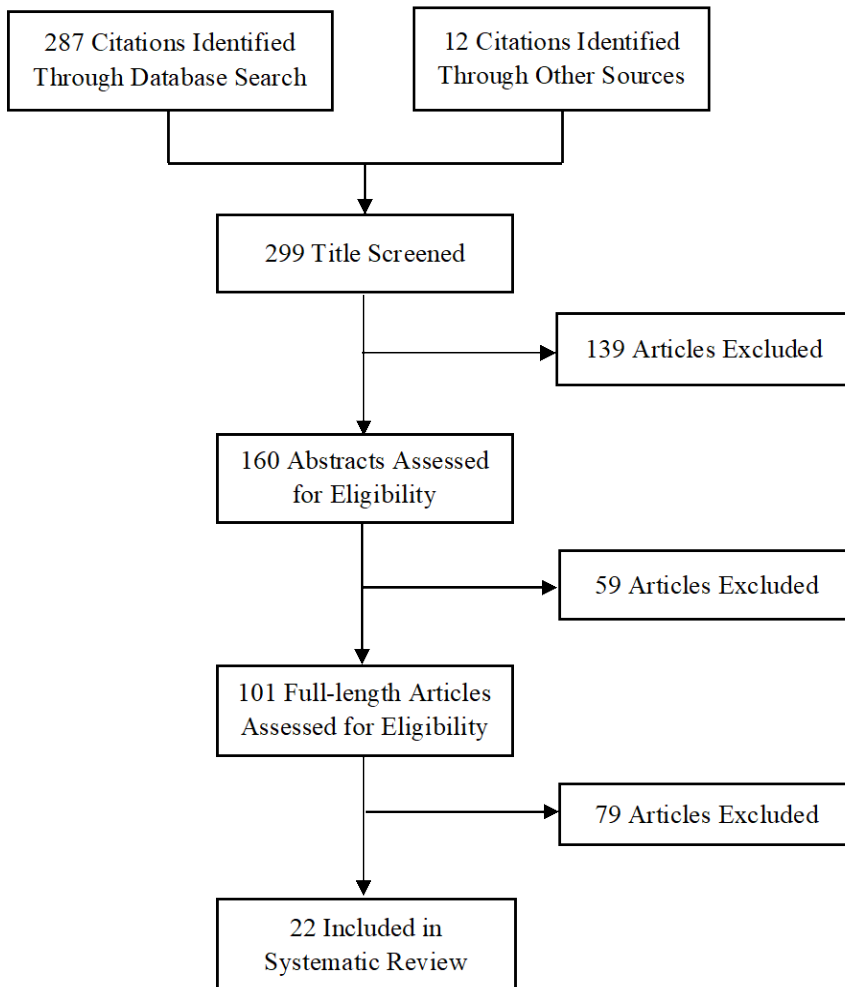
Appendix Figure 5. Flowchart of updated literature search and study selection for school closures.

Appendix Table 13. Basic characteristic of the studies included in school closures

Characteristic	No. studies (n = 101)
Type of influenza strain	
Seasonal	30
1918 pandemic	7
1968 pandemic	1
2009 pandemic	62
Seasonal and 2009 pandemic	1
Study setting	
Asia	30
Europe	26
America	38
Africa	1
Australia	6
Nature of closure*	
Outbreak report or teachers' strike	47
Planned holiday	28
Reactive closure	16
Preemptive closure	13
Duration of closure, d†	
7–13	40
14–20	24
$\geq$21	22
<7	13
Varied	8
Not clear	5

*Articles can contain different nature of closure at the same time
†Each study might have >1 dataset for which the durations of closure differed

Sixteen studies demonstrated that reactive school closure could be a useful control measure during influenza epidemics or pandemics, with impacts that included reducing the incidence and reducing the peak size (Appendix Table 14). Several studies reported a reduction in number of confirmed or ILI cases (*36,37,39,41,45,47,48*). One study also showed a reduction in total infected cases by 32.7% (total reduced number of cases from 127.1 to 85.5) (*44*). Another observational study suggested a reduction in the peak of the epidemic curve by 24% during the 4-day closure and also a reduction of the total number of infected students by 8% (*40*). However, 2 observational studies in China did not identify a significant difference for total attack rate between the control (school closure not implemented) and intervention group (school closed) (*34,35*). Two studies in the United States showed that absenteeism was lower after school reopening compared with before school closure (*42,43*).

The effectiveness of school closures can also be assessed by evaluating the transmission rate (i.e., reproduction number. Hens el al. estimated a reduction of the reproduction number from 1.33 (95% CI 1.11–1.56) to 0.43 (95% CI 0.35–0.52) after school closure (*38*). An observational study from Japan reported that school closure was more effective than class closure (dismissal of that particular class with substantial increase in influenza incidence) (*48*). In another study from Japan, a 2-day school closure in the outbreak situation (after a 10% of absentee occurrence in a school) was associated with the interruption of an outbreak within a week (*46*). One detailed study of transmission in a school in Pennsylvania identified no effect of the reactive closure that was implemented when 27% of students already had symptoms (*33*).

Effectiveness of preemptive school closure was studied in 13 articles (Appendix Table 15). A study showed that preemptive school closure had an advantage to delay the epidemic peak for more than a week, affect the modeled mean peak, and reduce overall attack rate from 9.7% to 8.6% (*49*). Bootsma et al. estimated that early and sustained interventions, including school closures, reduced the overall mortality rate by <25% in some cities (*50*). Hatchett et al. (*57*) and Markel et al. (*5*) also examined NPIs during the 1918–19 pandemic and reported that the combined use of NPIs, including school closures, were able to delay the time to peak mortality and to reduce peak and overall mortality rates (*5,57*).

One study estimated a 29%–37% reduction in influenza transmission by the 18-day period of mandatory school closures and other social distancing measures including closure of restaurants and theaters, and cancellation events (*52*). A study in Mexico City estimated that effective reproduction ratio declined from 1.6 before closure to less than 1 during closure (*55*). Wu et al. estimated that the reproduction number was reduced from 1.7 to 1.5 during the pre-

emptive closures and to 1.1 during the rest of the summer holiday (*60*). One study in Mexico showed a 80% reduction of contact rate during closure period and a subsequent planned holiday (*58*). However, closing kindergartens and primary schools for 2 weeks in Hong Kong did not show any significant effect on community transmission, although the incidence remained low after the peak during preemptive closure (*54*).

Twenty-eight studies monitored the change of influenza incidence across planned school holidays, for example the scheduled winter holiday each year, to estimate the impact of school closure on influenza transmission (Appendix Table 16). Of these studies, 8 showed that planned holidays could reduce influenza transmission (*58,61,63,69,70,72,81,85*). One study demonstrated that school holidays reduced the reproductive number R_0 of influenza A(H1N1)pdm09 by 14%–27% in different regions of India compared with a nonholiday period (*61*). One study also reported an association of school holiday with a reduction of 63% to 100% in transmission in Canada (*70*). Another study reported a reduction of R_0 from 1.25 to 0.79 during the 8 days-national holidays in China, but reported that the 8-week summer school holiday had a limited effect on incidence of ILI (*85*). Two studies in the United Kingdom and Mexico showed that school closures could reduce contact rate by around 48%–80% (*58,63*). Two studies in Belgium and the Netherlands suggested that holidays delayed the epidemic peak by >1 week and reduced the peak incidence by 4%–27% (*77,82*). A study from the United States showed that absenteeism in Adrian reduced by ≈6% (*79*), whereas Rodriguez et al. reported no difference between closed schools and those did not close (*80*).

Observational studies also reported a reduction in incidence of influenza associated with planned school holidays (*45,47,62,64–68,71,72,74–76,78,81,83,84*). Studies showed that summer or winter holidays were associated with the reduction of ILI incidences by showing significant changes of ILI incidence rate ratios of school children to adults during the breaks (*65,67,75*). A study based on national surveillance data in France showed that routine school holidays prevented 18% of seasonal influenza cases (18%–21% in children) (*64*). Another study in Japan estimated a 38% reduction in number of medically attended clinical ILI cases (*74*). Wheeler et al. suggested that planned holidays could prevent or delay potential influenza cases among school-age children by ≈42% (*83*). In comparison, a systematic review of simulation studies which review the effects of school closures on influenza outbreaks found that this intervention can be a useful control measure during an influenza pandemic (*133*).

Appendix Table 14. Summary of studies included in the review of reactive school closures

Author, Year	Reduce peak	Reduce overall attack rate	Reduce incidence	Reduce duration	Reduce transmission	Reduce Absenteeism
Cauchemez S, 2011 (*33*)	_	_	_	_	Reproduction number remained unchanged during school closure and after the reopening of school (R = 0.3)	_
Chen T, 2017 (*34*)	_	Total attack rate of 1–3 week of school closure were close to that for no intervention	_	Duration of outbreak was prolonged	_	_
Chen T, 2018 (*35*)	_	Total attack rate of 1–3 week of school closure were close to that for no intervention	_	Duration of outbreak was prolonged	_	_
Davis BM, 2015 (*36*)*	_	_	ILI rate ratio changed from 3.13 (3 weeks before peak), to 2.75 (at peak) and 1.79 (3 weeks after the peak)	_	_	_
Egger JR, 2012 (*37*)	_	_	7.1% reduction in ILI case over the outbreak period	_	_	_
Hens N, 2012 (*38*)	_	_	_	_	Influenza case reproduction number decreased from 1.33 (during outbreak before school closure) to 0.43 (after school closure)	_
Janjua NZ, 2010 (*39*)	_	_	Daily number of ILI cases declined during school closure	_	_	_
Kawano S, 2015 (*40*)^	Number of infected students in a school closure decreased by 24% at its peak	Cumulative number of infected students decreased by 8.0%	_	_	_	_
Loustalot F, 2011 (*41*)	_	_	Incidence remained low during closure	_	_	_
Miller JC, 2010 (*42*)	_	_	_	_	_	Absenteeism was lower after reopening compared with before closure
Russell ES, 2016 (*43*)	_	_	_	_	Closing schools after a widespread ILI activity did not reduce ILI transmission	Absenteeism changed from 1% (baseline), to 3.62% (during school closure), and 0.68% (after school reopening)

Author, Year	Reduce peak	Reduce overall attack rate	Reduce incidence	Reduce duration	Reduce transmission	Reduce Absenteeism
Sato T, 2013 (*44*)	_	Total number of infected persons decreased from 127.1 to 85.5; the maximum number of infected cases decreased from 63.7 to 53.1	_	_	_	_
Sonoguchi T, 1985 (*45*)	_	_	Number of cases declined from 16 on the day before closure to almost 13, 5, and 0 on the three days of closure in high school	_	_	_
Sugisaki K, 2013 (*46*)	_	_	_	Outbreak duration decreased by 4.98 d if the class is closed for 2 d upon the observed 10% ILI-related absentee rate	_	_
Uchida M, 2011 (*47*)			Incidence declined during closure period			
Uchida M, 2012 (*48*)^^	_	_	At elementary school, subsequent peak of H1N1 case showed up despite school or class closure (Figure 1); at junior high school, school closure significantly reduced the number of H1N1 case but not in class closure (Figure 2)	_	_	_

ILI: fever plus cough and/or sore throat
*ILI rate ratio is compared at school district with 51%–100% school being closed vs. district with 1%–50% of school being closed.
^Author mentioned the recommended period of school closure is >4 d
^^Closure duration is significantly related with the number of cases within the 7-d of school opening

Appendix Table 15. Summary of studies included in the review of pre-emptive school closures

Author, Year	Reduce peak	Reduce overall attack rate	Delay time to peak	Reduce incidence	Reduce transmission
Bolton, 2012 (*49*)	_	Overall attack rate decreased from 9.7% to 8.6%*	Epidemic peak would be delayed by over a week	_	_
Bootsma MC, 2007 (*50*)#	Earlier intervention may reduce peak mortality rate	Earlier intervention might reduce total mortality rate	_	_	_
Caley P, 2008 (*51*)#	_	_	_	_	Transmission reduced by 38% during period of social distancing

Author, Year	Reduce peak	Reduce overall attack rate	Delay time to peak	Reduce incidence	Reduce transmission
Chowell G, 2011 (*52*)#	_	_	_	_	Reproduction number decreased from 2.2 (before school closure) to 1.0 (during school closure); transmission rate is estimated to reduce by 29.6% during the intervention period
Copeland DL, 2013 (*53*)	_	_	_	Incidence rate of ARI increased from 0.6% (before closure), to 1.2% (during school closure) and dropped to 0.4% (after school reopening)	_
Cowling BJ, 2008 (*54*)^	_	_	_	_	Not found a substantial effect on community transmission
Cowling BJ, 2010 (*56*)^	_	_	_	_	The estimated reproduction number changed from 1.5 (initial peak) to below 1 (during pre-emptive closure), and fluctuated between 0.8 and 1.3 through the school vacations
Cruz-Pacheco G, 2009 (*55*)#	_	_	_	Incidence increased to peak then decreased gradually during closure period	Effective reproductive ratio R(t) declined from 1.6 before to <1 during closure
Hatchett RJ, 2007 (*57*)#	Earlier intervention reduced peak weekly excess P and death rate	_	_	_	_
Herrera-Valdez MA, 2011 (*58*)#	_	_	_	_	Reduced contact rates by around 80% during closure period
Markel H, 2007 (*5*)#	Earlier intervention reduced peak excess death rate	Earlier and increased duration of intervention reduced total excess death	Earlier interventions increased time to epidemic peak	_	_
Tinoco Y, 2009 (*59*)	_	_	_	Number of ILI cases decreased throughout closure period	_
Wu JT, 2010 (*60*)^					The reproduction number was reduced from 1.7 to 1.5 during the pre-emptive closures and to 1.1 during the rest of the summer holiday

ARI: Presence of at least 2 of the following symptoms: fever, cough, sore throat, or runny nose
ILI: fever plus cough and/or sore throat
#School closure combined with other interventions
^Pre-emptive closure followed by planned holidays
*Assuming schools were closed for 4 weeks and the attack rate in children was 3-fold higher than in adult

Appendix Table 16. Summary of studies included in the review of planned holidays

Author, Year	Reduce peak	Delay peak	Reduce overall attack rate	Reduce incidence	Reduce transmission	Reduce absenteeism
Ali ST, 2013 (*61*)	_	_	_	_	Reproduction number reduced by 14%–27% in different regions of India	_
Baguelin M, 2010 (*62*)	_	_	_	Incidence decreased throughout the closure period	_	_
Birrell PJ, 2011 (*63*)	_	_	_	_	Reduce contact rate among 5–14 y old by 72% (summer holiday) and 48% (half term holiday)	_
Cauchemez S, 2008 (*64*)	_	_	_	Routine school holidays prevented 18% of seasonal influenza cases (18%–21% in children)	_	_
Chowell G, 2011 (*66*)	_	_	_	Number of confirmed cases declined throughout closure period	_	_
Chowell,G, 2014 (*65*)*	_	_	_	Schoolchildren-to-adult ratios decreased by 40%–68% during the 2-week period immediately preceding the winter break	_	_
Chu Y, 2017 (*67*)	_	_	_	ILI incidence rate ratio of children 5–14 years of age (school children) to adult (aged above 60) decreased by 13.3% during summer break	_	_
Davies JR, 1988 (*68*)	_	_	_	Clinical influenza cases increased during closure period	_	_
Eames KT, 2012 (*69*)	_	_	_	_	The initial growth rate of the epidemic during holidays would be 35% lower than during term time (from 1.57 to 1.07)	_
Earn DJ, 2012 (*70*)	_	_	_	_	Reduction in transmission rate in school-age children was 63%, 100% and 86% as a result of schools closing for the summer in Calgary, Edmonton and the Province of Alberta as a whole respectively	_
Evans B, 2011 (*71*)	_	_	_	Estimated number of ILI cases declined during school holiday	_	_
Ewing A, 2017 (*72*)**	_	Figure 5A suggested a peak delay	_	Figure 5B illustrated a reduction of influenza incidence	Influenza transmission decreased by ≈15% (from 1.1 to 0.9) in most seasons	_

Author, Year	Reduce peak	Delay peak	Reduce overall attack rate	Reduce incidence	Reduce transmission	Reduce absenteeism
					and decreased to <1 immediately following Christmas	
Flasche S, 2011 (*73*)	–	–	–	–	No evidence found of a relationship between the effective reproduction number and the start of school holidays	–
Fujii H, 2002 (*74*)	–	–	–	Number of ILI cases decreased by 38% during the first week of closure (from 191 to 118 cases), then increased to 173 cases during the second week of closure	–	–
Garza RC, 2013 (*75*)	–	–	-	ILI incidence rate ratio reduced by 37% among children 5–14 y of age during the week after the winter school break	–	–
Herrera-Valdez MA, 2011 (*58*)#	–	–	–	–	Reduced contact rates by around 80% during closure period	–
Louie JK, 2007 (*76*)	–	–	–	ILI incidence declined throughout closure; laboratory-confirmed declined slightly first, then increased	–	–
Luca G, 2018 (*77*)^	Peak incidence reduced by 4%	All holidays delay the peak time of 1.7 weeks	Epidemic size reduced by ≈2%	–	–	–
Merler S, 2011 (*78*)^^	–	–	–	Incidence decreased during closure	–	–
Monto AS, 1970 (*79*)	–	–	–	–	–	Absenteeism reduced by ≈6% in Adrin
Rodriguez CV, 2009 (*80*)	–	–	–	–	–	No difference in post-break absenteeism in schools on holidays compared with schools that remained open at the same times (relative rate = 1.07, 95% CI = 0.96–1.20)
Smith S, 2011 (*81*)	–	–	–	Consultation rates decreased in school-age children	Transmission of influenza may be interrupted in that school-age group	–
Sonoguchi T, 1985 (*45*)	–	–	–	Case number remained low during closure period in middle school	–	–

Author, Year	Reduce peak	Delay peak	Reduce overall attack rate	Reduce incidence	Reduce transmission	Reduce absenteeism
Te Beest DE, 2015 (*82*)	Epidemic peak is lowered by 27%	Peak is delayed for ≈1 week	_	_	_	_
Uchida M, 2011 (*47*)	_	_	_	Incidence declined during closure period	_	_
Wheeler CC, 2010 (*83*)	_	_	_	Prevent or delay around 42% of potential influenza cases among school age children.	_	_
Wu J, 2010 (*84*)	_	_	_	Cumulative incidence of confirmed cases increased during school closure	_	_
Yu H, 2012 (*85*)	_	_	_	_	Reproduction number changed from 1.25 (before National Day holiday), to <1 (during that holiday), and 1.23 (after that holiday); National day holiday reduced the reproduced number by 37%	_

*Decrease in ratio is caused by a decrease in ILI rates among schoolchildren and the average reduction in ILI incidence among schoolchildren in the 2 weeks during the winter break compared with the 2 weeks before
**The holiday model combined the changes associated with both the school closure and travel models
^All holidays included Fall holiday, Christmas holiday, Winter holiday and Easter holiday
^^Mainly planned holidays, some reactive closures
#School closure combined with other interventions

Appendix Table 17. Summary of outbreak reports and teachers' strike studies included in the review of school closures

Author, Year	Outcome
Armstrong C, 1921 (*86*)	Number of cases peaked on the day following closure and declined thereafter
Baker MG, 2009 (*87*)	Start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic.
Briscoe JH, 1977 (*88*)	Number of clinical cases declined during closure
Calatayud L, 2010 (*89*)	Cases decline after the half way of school closure
Carrillo-Santisteve P, 2010 (*90*)	Number of confirmed and probable cases declined during closure
Cashman P, 2007 (*91*)	A planned school closure may have contributed to controlling the outbreak without quantitative information
Chieochansin T, 2009 (*92*)	Laboratory confirmed cases declined throughout period of closure
Cohen NJ, 2011 (*93*)	Number of respiratory illness cases were lower on the first day of closure compared with previous days, increased during closure and then declined.
Danis K, 2004 (*94*)	Number of ILI cases declined during closure period
Echevarria-Zuno S, 2009 (*95*)	Epidemic continued while schools were closed and peaked around 1 week after closure
Effler PV, 2010 (*96*)	Number of confirmed cases declined during closure period
Engelhard D, 2011 (*97*)	ILI rate peaked and declined during closure
Farley TA, 1992 (*98*)	Absenteeism remained low after school reopening
Glass RI, 1978 (*99*)	School absenteeism was lower after the holiday than before
Gomez J, 2009 (*100*)	Number of pneumonia cases decreased from 130 cases at peak to around 40 during closure
Grilli EA, 1989 (*101*)	During the mid-term break there were a further 15 ILI cases (daily cases not provided)
Guinard A, 2009 (*102*)	No further cases during school closure period, but epidemic appear to be over before the school was closed
Health Protection Agency West Midlands H1N1v Investigation Team, 2009 (*103*)	Confirmed number of cases declined during closure period
Heymann A, 2004 (*104*)*	Significant decreases in the rate of diagnoses of respiratory infections (42%), visits to physician (28%) and emergency departments (28%) and medication purchases (35%)
Heymann AD, 2009 (*105*)*	Decease in ratio of 14.7% for 6–12 y old associated with teachers' strike
Hsueh PR, 2010 (*106*)	Number of class suspensions or school closure generally associated with the number of hospitalizations
Huai Y, 2010 (*107*)	Number of confirmed cases peak at 30 cases on the first day of closure, then declined during closure period
Janusz KB, 2011 (*108*)	Absenteeism changed from 8% (baseline), to 15% (2 d before school outbreak), and 13% (post-school outbreak)
Johnson AJ, 2008 (*109*)	Number of parentally-reported ILI cases decline because of school closure
Jordan EO, 1919 (*110*)	Incidence declined from 19 cases to 15 cases the following week in elementary school, and declined from 16 to 5 cases in high school
Kawaguchi R, 2009 (*111*)	Number of confirmed cases declined throughout closure period
Lajous M, 2010 (*112*)	Planned holiday was followed by a slight decrease in ILI case numbers
Leonida DDJ, 1970 (*113*)	Absenteeism continued decline during second school closure
Lessler J, 2009 (*114*)	Both confirmed H1N1 influenza and self-reported ILI declined through closure period
Leung YH, 2011 (*115*)	Number of laboratory-confirmed cases increased during first two days of closure and then declined
Lo JY, 2005 (*126*)	Change in proportion of positive specimens were 50%–100% lower in April-June than the average because of community control measures
Marchbanks TL, 2011 (*116*)	Number of ILI cases increased during first two days of closure and then declined
Miller DL, 1969 (*117*)	In children aged 5–14 y, rates of influenza declined during the Christmas holidays
Nishiura H, 2009 (*118*)	Number of laboratory confirmed cases declined throughout the closure
Olson JG, 1980 (*119*)	School absenteeism (all-cause) declined in Girls Teachers' Colleges Primary School; absenteeism very similar before and after closure in Taipei American School
Paine S, 2010 (*120*)	Case numbers peaked and declined during holiday, effective reproduction number declined before holiday and continued to decrease during the holiday
Petrovic V, 2011 (*121*)	Weekly incidence rate of ILI and the number of hospitalized cases decreased after the school closure
Poggensee G, 2010 (*122*)	Practice index was associated with vacation density
Rajatonirina S, 2011 (*123*)	Only few cases continued to occur during closure period
Shaw C, 2006 (*124*)	Absenteeism was lower after closure than before closure in both reactive closure and planned holiday
Shimada T, 2009 (*125*)	Number of new confirmed cases decreased after school closures
Smith A, 2009 (*128*)	Number of ILI cases decreased during closure period
Strong M, 2010 (*129*)	Number of self-reported ILI cases decreased during closure period
van Gageldonk-Lafeber AB, 2011 (*130*)	Possible reduced incidence, or slowed epidemic growth
Wallensten A, 2009 (*131*)	Absenteeism almost not changed before and after closure
World Health Organization, 2009 (*127*)	School absenteeism in the following weeks did not increase after school reopening
Winslow CEA, 1920 (*132*)	Cities with school closures had higher deaths rates; timing and duration of closure were not stated

*Articles related to teachers' strike

Workplace Measures and Closures

Terminology

Workplace measures refers to the methods which can reduce influenza transmission in the workplace, or on the way to and from work, by decreasing frequency and length of social interactions. Workplace closure is the closure of workplaces when virus transmission is observed in the workplace, or an early planned closure of workplaces before influenza transmission initiates.

Search Strategy

The latest systematic review to review the effects of workplace measures in reducing influenza virus transmission was published by Ahmed et al. in 2018 (*134*). To update the systematic review, we conducted additional search in PubMed, Medline, EMBASE, and CENTRAL to identify literature available from January 1, 2017 through September 27, 2018. Workplace measures include teleworking, flexible leave policies, working from home, weekend extension, staggered work shifts, and social distancing at workplaces. All randomized controlled trial, epidemiologic study or simulation study in nonhealthcare workplaces were included in this review. Reviews, commentaries, editorial articles, studies on workplace closure, and studies on generic social distancing irrelevant to workplace were excluded from our review. The following outcomes were extracted from the studies: cumulative attack rate, peak attract rate, occurrence of peak, and others. Two reviewers (H.G. and J.X.) worked independently (Appendix Table 18).

For workplace closure, PubMed, Medline, EMBASE, and CENTRAL were searched to identify literature available from 1946 through September 17, 2018. No language limits were applied to the literature search but papers in languages other than English were excluded in screening. The inclusion criteria included randomized controlled trials, epidemiologic studies and simulation studies reporting the effectiveness of workplace closure in nonhealthcare settings, as well as the combination of workplace closure and other NPIs. The exclusion criteria included the following: studies in healthcare settings; studies that do not have specific data related to workplace closure; reviews, letters, news or summary articles; studies related to avian influenza. Two reviewers (H.G. and E.S.) independently screened titles, abstracts and full texts to identify eligible articles (Appendix Table 19).

Appendix Table 18. Search strategy for workplace measures

Search terms	Search date	Reviewers
#1: "telework" OR "leave" OR "social mixing" OR "social distancing" OR "community mitigation" OR "non-pharmaceutical" OR "nonpharmaceutical" #2: "influenza" OR "flu" #3: #1 AND #2	28 September 2018	H.G., J.X.

Appendix Table 19. Search strategy for workplace closures

| Search terms	Search date	Reviewers
#1: "workplace" OR "work site" OR "business" OR "organization" OR "office"	18 September 2018	H.G., E.S.
#2: "closure" OR "close"		
#3: "influenza" OR "flu"		
#4: #1 AND #2 AND #3		

Findings

The most recent systematic review was published in 2018, in which Ahmed et al. (*134*) identified 15 epidemiologic or simulation studies (from 14 articles) on workplace measures. In the additional search, 81 articles were identified from the databases and 1 article from other sources, resulting in 82 articles for title screening. Ten full-length articles were assessed for eligibility, and 3 additional articles were identified (Appendix Table 20). A total of 18 studies (17 articles) were included in our systematic review. The flowcharts of study selection are shown in Appendix Figures 6, 7.

There were 6 epidemiologic studies among the 18 included studies (*29,135–139*). A cross-sectional study interviewed randomly selected US adults from the Knowledge Networks online research panel, and showed that persons who cannot work from home (for 7–10 days) were more likely to have ILI symptoms compared with those who could (*135*). Another cohort study suggested that respondents who could work from home had a 30% lower rate of attending work with severe ILI symptoms compared with employees who cannot, suggesting work from home may be able to reduce employee-to-employee transmission (*137*). A cohort study in Singapore estimated that enhanced surveillance and segregation of work units into smaller working subgroups had significantly lower serologically confirmed infections compared with subgroups using the standard pandemic plan (17% vs 44%) (*136*). An intervention study evaluated the effectiveness of voluntary waiting at home on full pay against influenza A(H1N1)pdm09 transmission in workplaces showed an overall risk reduction by 20% (*29*). Piper et al. (*139*) and Asfaw et al. (*138*) used the data from nationally representative survey in the United States and showed that adults with paid sick days had higher probability of staying at home and thus reduced face-to-face transmission in the workplace. The remaining 12 studies were simulation studies reviewed by Ahmed et al. (*134*),and suggested that workplace measure alone reduced the cumulative attack rate by 23%, as well as delaying and reducing the peak influenza attack rate (*10,11,140–148*).
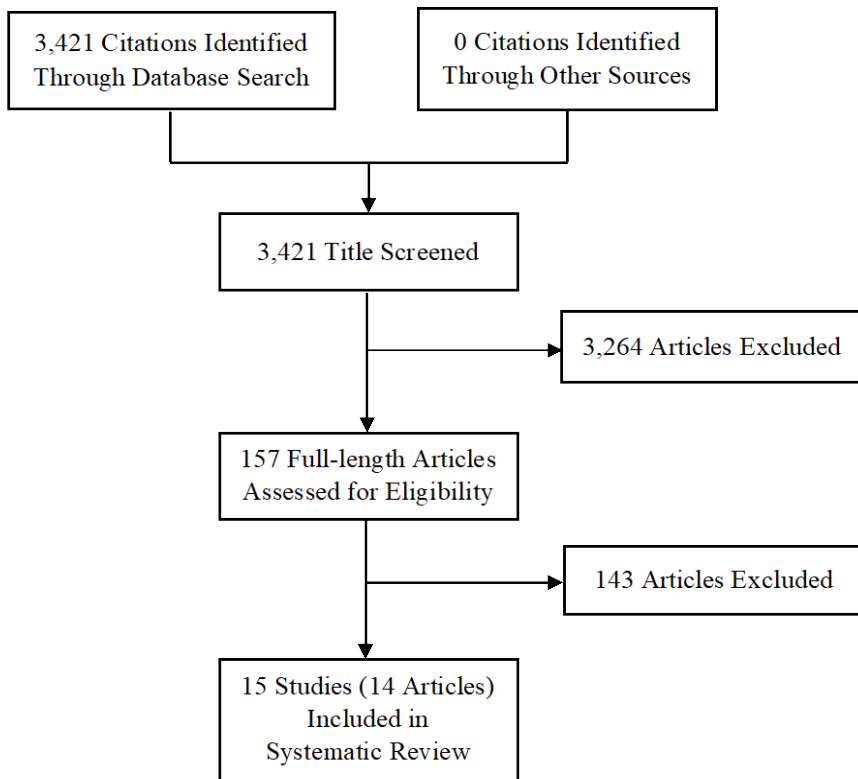
Appendix Figure 6. Flowchart of systematic review by Ahmed et al. (*134*).
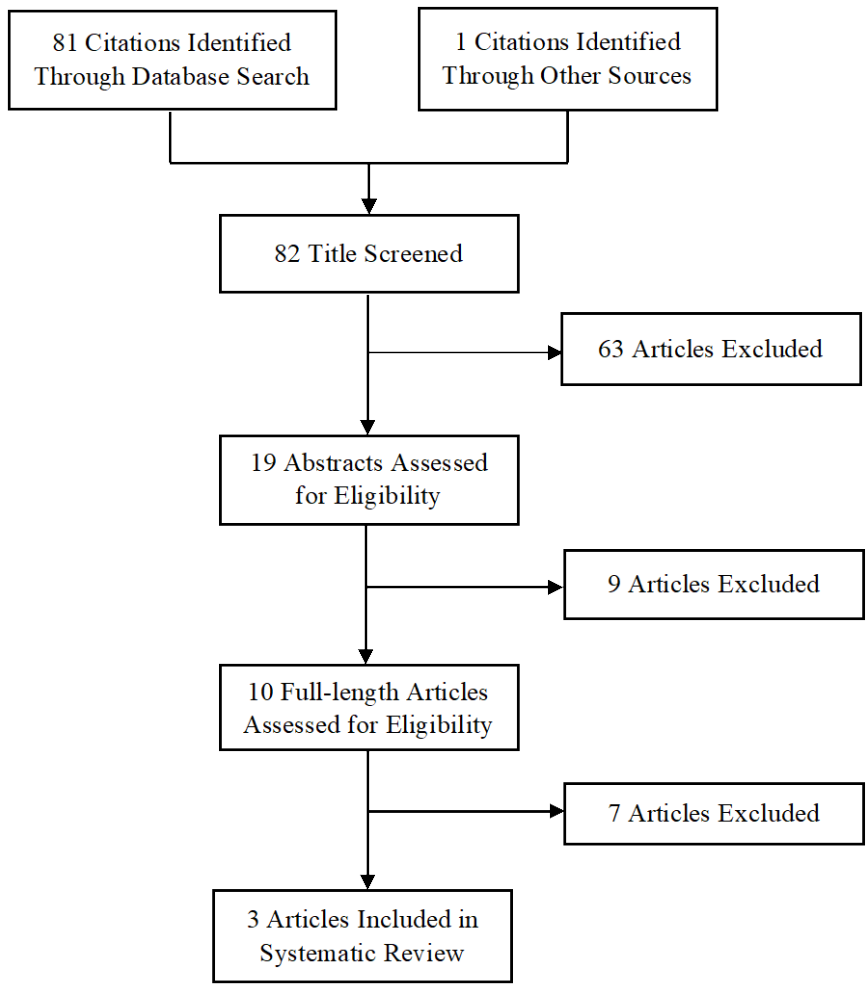
Appendix Figure 7. Flow chart of updated literature search and study selection for workplace measures.

Appendix Table 20. Summary of updated studies included in the review of workplace measures*

Study	Study design	Population and setting	Intervention	Comparison	Outcome
Asfaw A, 2017 (*138*)	National representative survey	Approximately 71,200 persons in the United States	Single: PSL	Without PSL	Employees with PSL had a 32% higher probability to stay at home than workers without PSL, which might benefit the reduction of transmission of influenza
Miyaki K, 2011 (*29*)	Intervention study	Two sibling companies (Cohort 1 n = 6,634, Cohort 2 n = 8,500) in Kanagawa Prefecture, Japan	Single: Voluntary waiting at home on full pay if a household member showed development of ILI	Continue to work in office even when a family member showed development of ILI	Intervention could reduce around 20% overall infection risk in the workplace
Piper K, 2017 (*139*)	National representative survey (3 rounds of interviews in 2009)	12,044 employees over 16 y old in the United States	Single: PSL	Without PSL	Persons with PSL were more likely to stay at home

*ILI, influenza-likw illness; PSL, paid sick leave

For workplace closure, 478 citations were identified through database search and other sources, of which 21 full-length articles were assessed for eligibility and 10 articles were selected for this systematic review. The flowchart of study selection is shown in Appendix Figure 8.
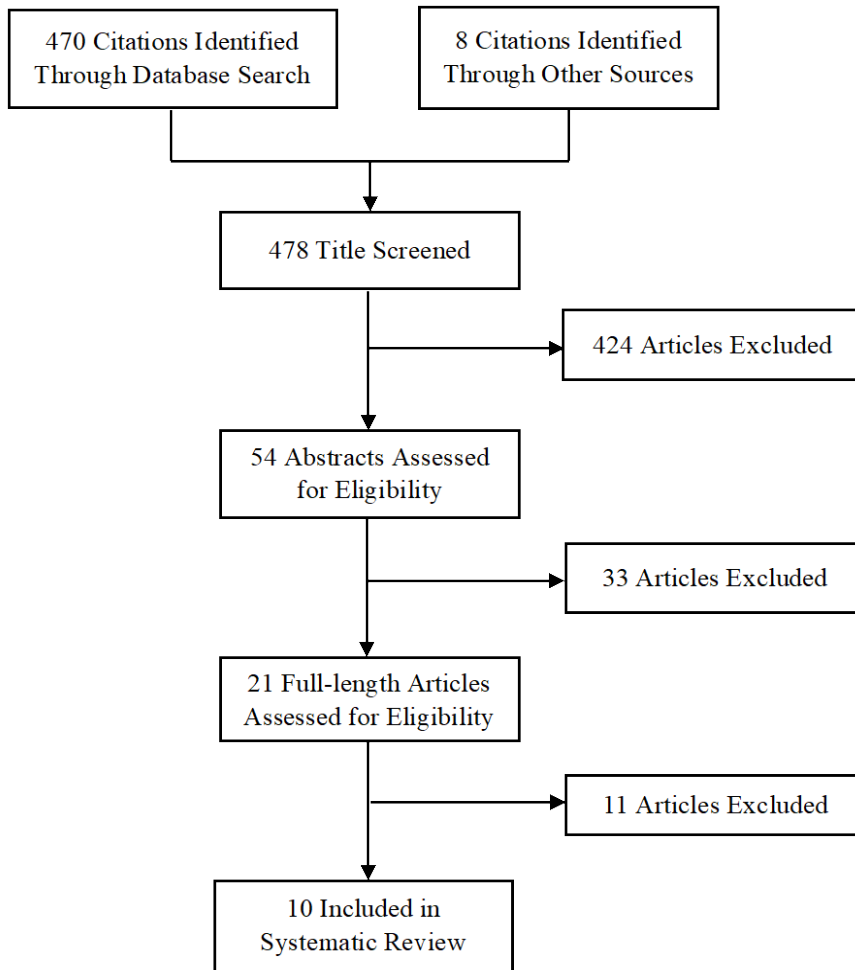
Appendix Figure 8. Flowchart of literature search and study selection for workplace closures.

Among these 10 studies, 8 of them studied combination of workplace closure with school closure, 1 targeted different single and multiple intervention strategies, and 1 evaluated the effectiveness of workplace closure alone (Appendix Table 21). All 10 studies were simulation studies and the main outcomes include the reduction of attack rate, peak number, and delay of epidemic peak.

Predicted Effects reduction

Most included studies suggested the reduction in attack rate, duration of infection or maximum case number. In the studies by Ferguson et al. (*7*) and Xia et al. (*149*), workplace closure resulted in a small reduction in cumulative attack rate, and Carrat et al. (*150*), Mao et al. (*151*), and Halder et al. (*152*) suggested an obvious decrease when assessing the effect of

combined interventions. A study by Carrat et al. simulated individual and community level model in France suggested a decrease of cumulative attack rate from 46.8% to 1.1%, assuming the basic reproduction number (R_0) of 2.07 (*150*). Mao et al. used an agent-based stochastic simulation model with R_0 1.3–1.4 in the United States and predicted a decrease of overall attack rates from 18.6% to 11.9% with 100% school closure (SC) and 10% workplace closure (WC), and from 18.6% to 4.9% with 100% SC and 33% WC (*151*). In addition, a study in Italy suggested that combining strategies including vaccination, prophylaxis and closure of schools, workplaces and public places could reduce the incidence from 50% to ≈15% (*153*).

However, a heuristic model using R_0 of 1.7 and 2.0 suggested a small reduction in cumulative attack rate but a more substantial reduction in peak attack rates (<40%) when 100% SC and 10% WC was implemented. It also suggested that the effectiveness could increase if 50% of workplaces were closed, at the same time resulting in a higher economic cost (*7*). A simulation model for the control of influenza in an isolated geographic region by Roberts et al. suggested that workplace closure as a single intervention could not prevent the epidemic ($R_0 = 2.0$) (*25*).

Delay the Time of Peak Occurrence

A simulation study using individual-based model suggested that nationwide closure of schools and workplaces for weeks would delay the time of peak occurrence by 5–8 days, and the effectiveness varied with the R_0 used (1.4, 1.7, and 2.0) (*154*). Rizzo et al. suggested implementing a combination of social distancing measures starting at 4 or 8 weeks of the beginning of a pandemic could delay the peak occurrence by 1 or 3 weeks (*155*). However, a study by Mao et al. estimated that 100% SC and 33% WC could speed up the peak by ≈1 week (*151*).

Appendix Table 21. Summary of studies included in the review of workplace closures*

Study	Influenza strain and transmissibility (R_0)	Study setting and population	Study design	Closure duration	Closure proportion	Closure threshold	Intervention	Comparison	Outcome
Carrat F, 2006 (*150*)	Future pandemic strain; $R_0 = 2.07$	General population in France (n = 10,000)	Simulation both individual and community level	NA	NA	5 infections/1,000 persons	SC + WC	No intervention	Mean accumulation infection rate reduced from 46.8% (42.3%–50.5%) to 1.1% (0.6%–2.1%)
Ciofi degli Atti ML, 2008 (*154*)	Future pandemic strain; $R_0 = 1.4, 1.7, 2$	General population in Italy (around 57 million)	Global SEIR model for importation of cases with an individual based model	4 weeks	NA	NA	SC + WC	No intervention	Nationwide closure could delay the peak occurrence by 5–8 d based on various scenarios
Ferguson NM, 2005 (*156*)	Future pandemic strain	Simulated population in Thailand	Stochastic, spatially structured, individual-based discrete time simulation model	NA	NA	NA	SC + WC + antiviral prophylaxis	NA	Interventions could eliminate the pandemic if R_0 is below 1.8
Ferguson NM, 2006 (*7*)	Future pandemic strain; $R_0 = 1.7, 2.0$	300 million in USA, 58.1 million in UK	Heuristic model	NA	Varied: 10%, 50%	NA	100% SC + varied WC (10%, 50%)	No intervention	100% SC + 10% WC could slightly reduce the cumulative attack rate, and might reduce the peak attack rate up to 40%. 50% of WC could further improve the effectiveness, albeit with a higher economic cost
Halder N, 2011 (*152*)	Future pandemic strain with H1N1 2009 characteristics; $R_0 \sim 1.3$	Albany, Western Australia (n = 30,000)	Individual-based simulation model	Varied: 2 weeks or 4 weeks or continuous	50%	NA	1) SC 2 weeks + 50% WC 2 weeks 2) SC 2 weeks + 50% WC 4 weeks 3) Continuous SC + 50% WC	No intervention	The three interventions reduced the attack rate by 34.5%, 37.4% and 79.7% respectively
Mao L, 2011 (*151*)	Future pandemic strain; $R_0 = 1.3–1.4$	Urbanized area of Buffalo, NY, USA (n = 985,001)	Agent-based stochastic simulations	NA	Varied: 10%, 33%	NA	1) 100% SC + varied (10%, 33%) WC; 2)100% SC + varied (10%, 33%) WC + preventive behavior	No intervention	1) Overall attack rates declined from 18.6% to 11.9% (10%WC) and 4.9% (33% WC) respectively 2) Overall attack rates reduced to 3.99% (10%WC) and 1.83% (10%WC) respectively
Merler S, 2006 (*153*)	Future pandemic strain; $R_0 = 1.7$	Central Italy (n = 12,489,619)	Individual-based simulation model	4 weeks	NA	20 symptomatic cases were detected	Vaccination + Prophylactic antiviral	No intervention	The incidence dropped from 50% to ≈15%

Study	Influenza strain and transmissibility (R_0)	Study setting and population	Study design	Closure duration	Closure proportion	Closure threshold	Intervention	Comparison	Outcome
							treatment + Quarantine measures (SC + WC + public places)		
Rizzo C, 2008 (*155*)	Future pandemic strain; $R_0 = 1.8$	National population in Italy (n = 56,995,744)	SEIR deterministic model with a stochastic simulation component	4 weeks	NA	2, 4, or 8 weeks after the start of the pandemic	Nationwide closure of all schools, public offices, and public meeting places	No intervention	Social distancing measures were not effective in reducing attack rate, but could delay the peak occurrence by 1–3 weeks
Roberts MG, 2007 (*25*)	Future pandemic strain; $R_0 = 1.1$, 2.0 and 3.0	Isolated geographic region (n = 1,000,000)	A model based on published parameters	N/	70%	NA	1) WC; 2) WC + SC; 3) WC + SC + antiviral treat + 70% home quarantine	No intervention	The single strategy of WC is not successful, the combination of all four strategies might prevent the epidemic
Xia H, 2015 (*149*)	Simulate H1N1; $R_0 = 1.35$, 1.40, 1.45, 1.60	Delhi, India (over 13 million)	Realistic individual-based social contact network and agent-based modeling	3 weeks	60%	Over 0.1% population are infected	Single WC	No intervention	Intervention could reduce the attack rate, peak number, and delay the time of peak occurrence. WC as a single intervention is the most ineffective method among vaccination, antiviral usage, SC, and WC

*NA, not available; SC, school closures; WC, workplace closures.

Avoiding Crowding

Terminology

Avoiding crowding refers to the measures to reduce influenza transmission in crowded areas (e.g., large meetings, conferences, and religious pilgrimages, national and international events).

Search Strategy

Literature available from 1946 through October 17, 2018 were identified from PubMed, Medline, EMBASE, and CENTRAL. Two reviewers (S.G. and E.S.) screened each title, abstract and article that fully met the criteria (Appendix Table 22). Both epidemiologic and simulation studies relevant to the effectiveness of avoiding crowding (e.g., cancellation or postponement of events and limitation of attendance) in public area are included. Studies that only reported outbreak events in a crowded area or perceptions on mass gathering without specific data related to the effectiveness of avoiding crowding; and reviews, letters, news, or summary articles were excluded.

Appendix Table 22. Search strategy for avoiding crowding

Search terms	Search date	Reviewers
#1: "event" OR "meeting" OR "sport" OR "concert" OR "pilgrimage" OR "park" OR "conference" OR "mass" OR "public" OR "community" OR "large" OR "general" OR "church"	October 18, 2018	H.G., E.S.
#2: "gather*" OR "crowd*"		
#3: "influenza" OR "flu"		
#4: #1 AND #2 AND #3		

Findings

We identified 3 studies for the systematic review after reviewing 815 titles and 121 abstracts identified from the 4 databases and other sources. Appendix Figure 9 shows the study selection process. Among these 3 articles, 2 were based on the 1918 influenza pandemic, and 1 focused on an influenza outbreak during the World Youth Day gathering in 2008 (details shown in Appendix Table 23).

Hachett et al. (*57*) and Markel et al. (*5*). reported a strong association between the early implementation of interventions and the mitigation of the 1918 pandemic. The study by Markel et al. (*5*) showed 3 major categories for NPI: SC, cancellation of public gatherings, and isolation or quarantine in 43 cities in the United States. SC combined with a ban on public gatherings was the most common intervention with a median duration of 4 weeks, which reduced significantly weekly excess death rate Early implementation led to greater delays in reaching peak mortality

rates (Spearman $\rho = -0.74$, p<0.001), lower peak mortality rates (Spearman $\rho = 0.31$, p = 0.02)

and lower total mortality rates (Spearman $\rho = 0.37$, p = 0.008) (5). There was a significant

association between increased duration of interventions and a reduction in the total mortality rate

(Spearman $\rho = -0.39$, p = 0.005) (5). Another study by Hatchett et al. also focused on the early

bans on public gathering and closure of public places in reducing the excess death rate (57). In

addition, during the 1-week long World Youth Day event in 2008, the group of youths who were

accommodated in a single large place (17.2%) had a significantly higher attack rate compared

with youths who lived in small classrooms (9.2%) (p<0.01) (157).

Appendix Table 23. Summary of studies included in the review of avoiding crowding

Study	Influenza	Intervention	Comparison	Outcome
Hatchett RJ, 2007 (57)	1918 Pandemic	Early church closure, theater closure and bans on public gathering	Cities with different timing and combination of non-pharmaceutical interventions	Associated with lower peak excess death rates (Spearman $\rho = 0.56$, $\rho = 0.56$, $\rho = 0.46$ separately)
Markel H, 2007 (5)	1918 Pandemic	Multiple: SC + cancellation of public gatherings + isolation and quarantine.	Cities with different timing, duration and combination of non-pharmaceutical interventions	Implemented earlier and longer duration are significantly associated with the reduction of influenza transmission
Staff M, 2011 (157)	World Youth Day 2008 pilgrims	Pilgrims was sub-divided into smaller groups and accommodated in classrooms for 1 week.	Pilgrims was accommodated as a large group in a gymnasium	The attack rate was significantly (p<0.01) higher among pilgrims accommodated in the gymnasium (17.2%) than those staying in the classrooms (9.2%)
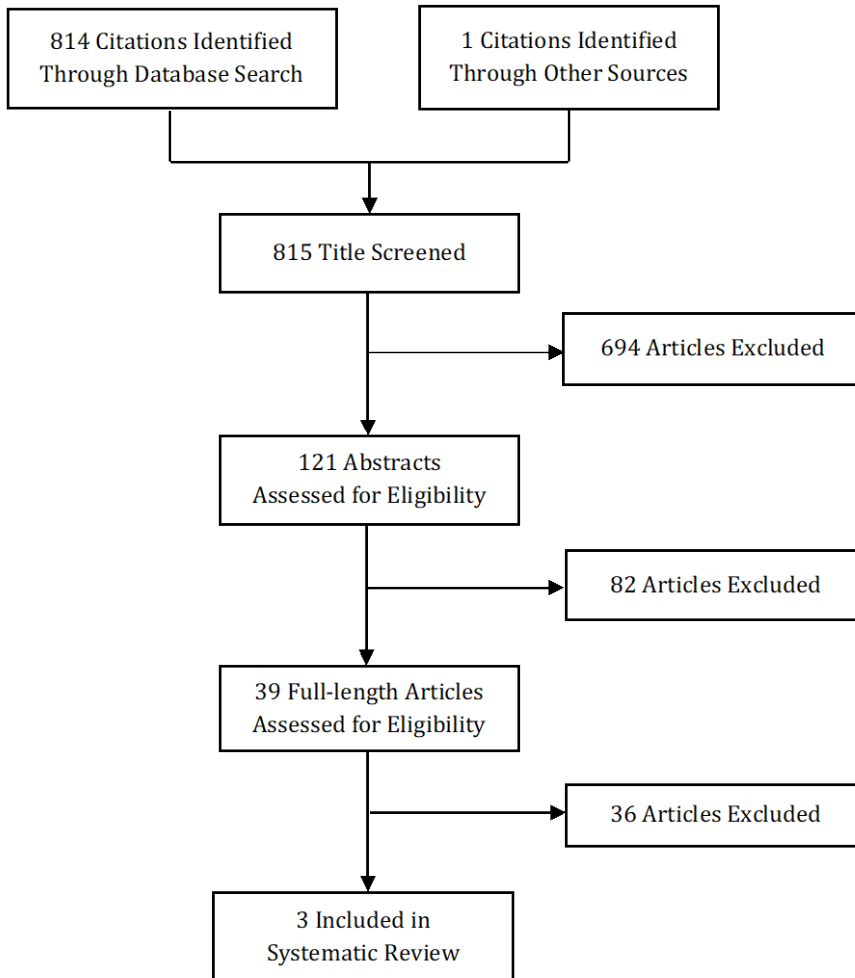
Appendix Figure 9. Flowchart of literature search and study selection for avoiding crowding.

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