GLOBAL INFLUENZA PROGRAMME

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

Annex: Report of systematic literature reviews

World Health Organization

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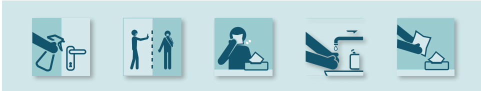

Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza

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Abbreviations and acronyms

ACH	air changes per hour
CI	confidence interval
EDR	excess death rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ILI	influenza-like illness
ITIS	infrared thermal image scanner
NPI	non-pharmaceutical intervention
PCR	polymerase chain reaction
PICTs	Pacific Island Countries and Territories
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	risk ratio
SC	school closure
UV	ultraviolet
WC	workplace closure
WHO	World Health Organization

Glossary

Contact tracing	Identification and follow-up of persons who may have come into contact with an infected person.
Closure	Halting the operation of an institution or business.
Isolation	Separation or confinement of a person who has or is suspected of having influenza virus infection, to prevent further infections.
Non-pharmaceutical /non-pharmacological interventions	Interventions that do not include pharmacological measures such as vaccines and antiviral drugs.
Personal protective measures	Measures to reduce personal risk of infection, such as hand washing and face masks.
Quarantine	Separation or restriction of the movement of persons who may be infected, based either on exposure to other infected people or on a history of travel to affected areas.
Movement restriction	Limitation on the movements of a person who has or is suspected of having an infection

EXECUTIVE SUMMARY

New influenza A viruses emerge in humans from time to time, causing global pandemics. The most recent influenza pandemic began in 2009 with the influenza A(H1N1)pdm09 virus. Public health measures against pandemic influenza include vaccines, antiviral drugs and non-pharmaceutical measures. Given that vaccines against novel pandemic strains are unlikely to be available in the early months of an influenza pandemic, and antiviral drugs are in short supply in many locations, non-pharmaceutical public health measures are often some of the most accessible interventions for community mitigation of a pandemic. Non-pharmaceutical interventions (NPIs) also have an important role in mitigating interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. These measures could reduce individuals' risk of infection, delay the epidemic peak, reduce the "height" of the epidemic peak, and spread cases over a long time period; each of these outcomes would contribute to reducing the overall impact of a pandemic or epidemic.

Here, we systematically review and evaluate the evidence base on the effectiveness and impact of community mitigation measures for pandemic and interpandemic influenza. This evidence base will contribute to updated public health guidelines for community mitigation measures for influenza. The scope of this review includes evidence on the effectiveness of interventions such as personal protective measures, environmental measures, social distancing measures, and travel-related measures. Consideration is also given to the feasibility of each intervention, including potential ethical issues.

We found that there is a limited evidence base on the effectiveness of non-pharmaceutical community mitigation measures. There are a number of high-quality randomized controlled trials demonstrating that personal measures (e.g. hand hygiene and face masks) have at best a small effect on transmission, with the caveat that higher compliance in a severe pandemic might improve efficacy. However, there are few randomized trials for other NPIs, and much of the evidence base is from observational studies and computer simulations. School closures can reduce transmission, but would need to be carefully timed to achieve mitigation objectives, while there may be ethical issues to consider. Travel-related measures are unlikely to be successful in most locations because current screening tools such as thermal scanners cannot identify presymptomatic and asymptomatic infections, and travel restrictions and travel bans are likely to have prohibitive economic consequences.

INTRODUCTION

Non-pharmacological interventions (NPIs) are often the most accessible interventions when a new pandemic influenza virus emerges and begins to spread, because of limited availability of antiviral drugs and delays in the availability of vaccines against the pandemic strain (1). These community mitigation measures may be able to slow the spread of infections in the community, delaying the peak in infections, reducing the size of the peak and spreading infections over a longer period of time (Fig. 1) (*2, 3*). Each of these consequences should contribute to reducing the overall impact of the epidemic or pandemic. Given that in some locations there could be limited surge capacity in hospitals (and particularly in intensive care beds), spreading infections over a longer time period could save lives, even if the total number of infections remained the same.

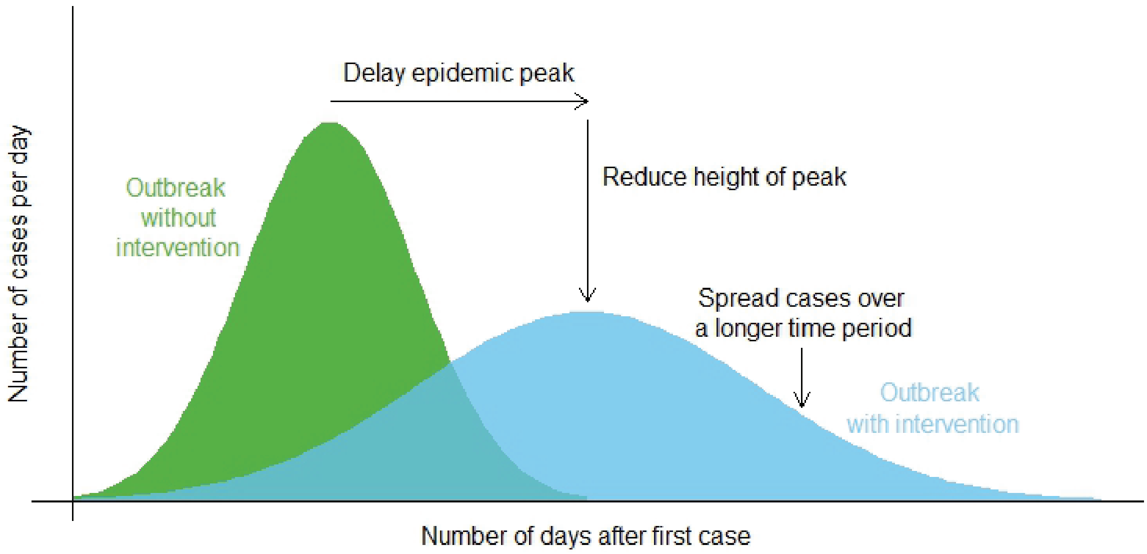


Fig. 1. Intended impact of non-pharmaceutical interventions on an influenza epidemic or pandemic by reducing person-to-person transmission

NPIs in non-health care settings usually focus on: reducing transmission by personal or environmental protective measures (e.g. hand hygiene); reducing the spread in the community populations (e.g. isolating and treating patients; closing schools and cancelling mass gatherings); limiting the international spread on travelling (e.g. travel screening and restriction); and public advice to the community (*4*). A number of health authorities have recently updated their reviews and guidelines on NPIs, including the United States (US) Centers for Disease Control and Prevention (CDC) (*2*), the European Centre for Disease Prevention and Control (*3*), the Australian Government Department of Health (*5*), the United Kingdom Department of Health (*6*), the Singapore Ministry of Health (*7*) and the Government of New Zealand (*8*).

This review examines the evidence base on each of the NPIs in community settings. While our focus is on the effectiveness of NPIs for mitigation of an influenza pandemic, the same measures may also be used in interpandemic influenza epidemics, which occur each winter in temperate locations and at varying times of the year in tropical and subtropical locations. In addition to NPIs in community settings, health authorities may also intervene in health care settings and systems, for example by establishing special influenza outpatient clinics, improving triage and isolation in hospitals, and cancelling non-essential surgeries. Health care system interventions are outside the scope of the present review of community mitigation measures.

The list of community mitigation measures is shown below. For each of the 18 listed NPIs, we first determined whether any systematic review had been published within the past 5 years (i.e. since January 2014), If there was a recently published review, we conducted a systematic review limited to studies published more recently than that review (starting from 1 year prior to the publication date), and updated that existing review. If we could not identify a systematic review of the NPI within the past 5 years, we conducted a full systematic review for the NPI. For the review of peer-reviewed articles, two independent reviewers screened all titles of studies identified by the search strategy for each of the NPIs, then reviewed the abstracts of the potentially relevant studies. If the studies described that NPI and its effectiveness against influenza transmission, the reviewers read the full-length text and extracted relevant data. Further discussion with a third reviewer was held if a consensus was not reached. We also evaluated the methodological quality of each of the studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (*9*), based on the question of whether NPIs can reduce influenza transmission in the community. The quality of evidence was ranked for each study as high, moderate, low or very low, based on its risk of bias, consistency, directness, precision of the results and publication bias. Hence, we set the highest priority on randomized controlled trials (RCTs), then on observational studies and finally on simulation studies. If RCTs were reported, as a general principle we did not review observational studies or simulation studies, and if observational studies were reported, as a general principle we did not review simulation studies.

This report describes the evidence base on the effectiveness of each NPI. The specific targets of the evidence include but are not limited to reducing transmission, delaying the peak of the epidemic, spreading out infections over a longer time period, and reducing the total number of infections. This review of the evidence base will support the development of guidance on the use of NPIs for community mitigation. The NPIs reviewed in this report are listed below.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
Personal protective measures	**Personal hygiene measures to reduce the risk of acquiring or spreading respiratory infections.**
1. Hand hygiene	A personal measure aiming to reduce influenza transmission via direct or indirect contact by washing hands with soap and water or alcohol-based hand cleaners.
2. Respiratory etiquette	A personal measure aiming to reduce influenza transmission via respiratory droplets by covering nose and mouth with disposable tissues while coughing or sneezing.
3. Face masks	A personal measure aiming to reduce influenza transmission by wearing face mask of different types, including home-made masks, surgical and medical masks, or respirators with higher filtration rates. Masks can be worn by symptomatic or exposed persons to reduce onwards transmission (source control), or by uninfected persons in the community to reduce their risk of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES	
NPI	**DEFINITION**
Environmental measures	**Environmental hygiene measures to reduce the risk of acquiring or spreading influenza within an area.**
4. Surface and object cleaning	Routine cleaning of frequently used surfaces and objects to reduce influenza transmission.
5. Other environmental measures	Other measures to reduce risk of influenza transmission through the environment.
Social distancing measures	**Social measures to reduce the risk of acquiring or spreading respiratory infections in various community settings (e.g. homes, workplaces, schools, health care settings etc.)**
6. Contact tracing	The identification and follow-up of persons who may have come into contact with an infected person, usually in combination with quarantine of identified contacts.
7. Isolation of sick individuals	Reduction in virus transmission from an ill person to others by confining symptomatic individuals for a defined period either in a special facility or at home.
8. Quarantine of exposed individuals	Isolation of individuals who contacted a person with proven or suspected influenza, or travel history to an affected area, for a defined period after last exposure. Quarantined cases may be isolated.
9. School closure	Closure of schools either when virus transmission is observed in the school or community, or an early planned closure of schools before influenza transmission initiates.
10. Workplace closure	Closure of workplaces when virus transmission is observed in the workplace, or an early planned closure of workplaces before influenza transmission initiates.
11. Workplace measures	Measures to reduce influenza transmission in the workplace, or on the way to and from work, by decreasing frequency and length of social interactions.
12. Avoiding crowding	Measures to reduce influenza transmission in crowded areas (e.g. large meetings, conferences, and religious pilgrimages, national and international events).
Travel-related measures	**Measures including the provision of travel health advice, screening of travellers and restriction of travellers.**
13. Travel advice	Official government travel advice with legal and economic implications.
14. Entry and exit screening	Screening travellers for influenza symptoms to reduce the number of infectious individuals entering or leaving a country with infection, respectively, in order to delay the international spread of infection.

LIST OF NON-PHARMACEUTICAL PUBLIC HEALTH MEASURES

NPI	DEFINITION
15. Internal travel restrictions	Prevent or limit influenza transmission by restricting travel within a country.
16. Border closures	Prevent influenza entering a country by restricting travel to or from an affected area, in order to delay the international spread of infection.

SUPPORTING EVIDENCE FOR NPIS

Search strategy

Systematic reviews of NPIs were conducted using four databases (PubMed, EMBASE, MEDLINE and Cochrane Library) and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy for each topic is given below.

MEASURES	SEARCH TERMS
1. Hand hygiene	#1: "hand hygiene" OR "hand washing" OR "handwashing" OR "hand-washing" OR "hand-wash" OR "hand wash" OR "handwash" OR "hand sanitize" OR "hand sanitizers" OR "hand sanitizer" OR "hand rub" OR "handrub" OR "hand rubbing" OR "hand cleansing" OR "hand cleans" OR "hand cleanser" OR "hand disinfectant" OR "hand disinfectants" OR "hand disinfection" OR "hand soap" OR "hand wipe" #2: "influenza" OR "flu" #3: #1 AND #2
2. Respiratory etiquette	#1: "respiratory hygiene" OR "cough etiquette" OR "respiratory etiquette" #2: "influenza" OR "flu" #3: #1 AND #2
3. Face masks	#1: "facemask" OR "facemasks" OR "mask" OR "masks" OR "respirator" OR "respirators" #2: "influenza" OR "flu" #3: #1 AND 2
4. Surface and object cleaning	#1: "surface" OR "surfaces" OR "object" OR "objects" OR "fomite" OR "fomites" OR "environment" OR "environmental" #2: "clean" OR "cleans" OR "cleaning" OR "cleanse" OR "cleansing" OR "disinfect" OR "disinfects" OR "disinfection" OR "disinfecting" OR "wipe" OR "wipes" OR "sanitize" OR "sanitizes" OR "sanitizing" OR "sanitation" OR "sterilize" OR "sterilizes" OR "sterilizing" OR "sterilization" OR "sterilise" OR "sterilises" OR "sterilising" OR "sterilisation" OR "decontaminate" OR "decontaminates" OR "decontaminating" OR "decontamination" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
5. Other environmental measures	UV light #1: "ultraviolet" OR "UVGI" OR "UV" OR "UVC" OR "far-UVC" OR "UV-C" #2: "influenza" OR "flu" #3: #1 AND #2 Ventilation and humidity #1: "ventilation" OR "temperature" OR "humidity" OR "environment" #2: "indoor" OR "room" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
6. Contact tracing	#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
7. Isolation of sick individuals	#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
8. Quarantine of exposed individuals	#1: "quarantine" #2: "influenza" OR "flu" #3: #1 AND #2
9. School closure	#1: "school closure" OR "class dismissal" OR "school holiday" OR "community mitigation" OR "social distancing" #2: "influenza" OR "flu" #3: #1 AND #2
10. Workplace closure	#1: "workplace" OR "work site" OR "business" OR "organization" OR "office" #2: "closure" OR "close" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
11. Workplace measures	#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
12. Avoiding crowding	#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" #2: "gather*" OR "crowd*" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3

MEASURES	SEARCH TERMS
13. Travel advice	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "advice" OR "restrict" OR "restriction" OR "prohibit" OR "prohibition" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
14. Entry and exit screening	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "screen" OR "screening" OR "entry screening" OR "exit screening" OR "entry-exit screening" OR "mass screening" OR "border screening" OR "detect" OR "detecting" OR "detection" #3: "influenza" OR "flu" #4: #1 AND #2 AND #3
15. Internal travel restriction	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "domestic" OR "internal" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" #4: "influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4
16. Border closure	#1: "travel" OR "traveler" OR "travelers" OR "traveller" OR "travellers" #2: "border" OR "international" #3: "restrict" OR "restriction" OR "prohibit" OR "prohibition" OR "limit" OR "limitation" OR "control" OR "closure" #4: influenza" OR "flu" #5: #1 AND #2 AND #3 AND #4

1. PERSONAL PROTECTIVE MEASURES

1.1. Hand hygiene

Terminology

The definitions of relevant hand hygiene practices and products, and common terminology, are shown in Table 1 below.

Table 1. Definitions of hand hygiene terms

TERM	DEFINITION
Hand hygiene practices	
Hand hygiene	A general term referring to any action of hand cleansing, e.g. handwashing, antiseptic handwash, antiseptic hand rub, or surgical hand antisepsis (*10, 11*)
Hand cleansing	Action of performing hand hygiene for the purpose of physically or mechanically removing dirt, organic material, and/or microorganisms (*10*)
Handwashing	Washing hands with plain or antimicrobial soap and water (*10*)
Antiseptic handwashing	Washing hands with soap and water, or other detergents containing an antiseptic agent (*10*)
Antiseptic handrubbing (or handrubbing)	Applying an antiseptic handrub to all surfaces of the hands to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices (*10, 11*)
Hand disinfection	Hand disinfection is extensively used as a term in some parts of the world and can refer to antiseptic handwash, antiseptic handrubbing, hand antisepsis / decontamination / degerming, handwashing with an antimicrobial soap and water, hygienic hand antisepsis, or hygienic handrub (*10*)
Hand hygiene products	
Alcohol-based (hand) rub (or hand sanitizer)	An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants (*10*)

TERM	DEFINITION
Antimicrobial (medicated) soap	Soap (detergent) containing an antiseptic agent at a concentration sufficient to inactivate microorganisms and/or temporarily suppress their growth. The detergent activity of such soaps may also dislodge transient microorganisms or other contaminants from the skin to facilitate their subsequent removal by water (*10*)
Antiseptic hand wipe	A piece of fabric or paper pre-wetted with an antiseptic used for wiping hands to inactivate and/or remove microbial contamination. They may be considered as an alternative to washing hands with non-antimicrobial soap and water but, because they are not as effective at reducing bacterial counts on health care workers' hands as alcohol-based handrubs or washing hands with an antimicrobial soap and water, they are not a substitute for using an alcohol-based handrub or antimicrobial soap (*10*)
Plain soap	Plain soap refers to detergents that do not contain antimicrobial agents or contain low concentrations of antimicrobial agents that are effective solely as preservatives (*11*)
Other	
Visibly soiled hands	Hands showing visible dirt or visibly contaminated with proteinaceous material, blood, or other body fluids (e.g. faecal material or urine) (*11*)

Methods

We conducted a review of systematic reviews. PubMed, Medline, EMBASE and CENTRAL were searched for reviews until 1 August 2018. Review selection criteria were systematic reviews within 5 years studying the effect of hand hygiene interventions on prevention of laboratory-confirmed influenza in non-health care settings, regardless of language.

After identifying the most recent published systematic review (see below), we updated the search done in that published review in the same four databases through to 14 August 2018 using the same search terms. Study selection criteria were RCTs comparing the effect of hand hygiene interventions with no intervention in laboratory-confirmed influenza prevention in community settings. Study participants or clusters of participants were assigned prospectively into intervention and control groups using random allocation. A community setting was defined as an open setting without confinement or special care for the patients. Articles describing any hand hygiene related interventions were included. No language limits were applied.

Because of the availability of a reasonable number of randomized trials of hand hygiene, we did not extend the search to observational studies, but we did note the findings from earlier systematic reviews of observational studies of hand hygiene (*12-14*).

After data extraction, quality assessment of the evidence was done for included studies based on the GRADE framework. The research question was to study the effect of hand hygiene intervention on laboratory-confirmed influenza prevention.

Two independent reviewers (ZX and ES) reviewed retrieved titles and subsequent relevant abstracts independently. Titles or abstracts with any one of the reviewers' decision to include were included in next step. After title and abstract screening, two reviewers reviewed the full text based on the selection criteria. Data extraction and evidence quality assessment were also done by the reviewers. If a consensus was not reached, further discussion was held or opinion was obtained from the third independent reviewer.

Risk ratios (RRs) and their 95% confidence intervals (95% CIs) were calculated to estimate the effect of hand hygiene intervention on prevention of laboratory-confirmed influenza. Heterogeneity of each pooled and subgroup analysis was assessed by I2 statistics. The overall effect of each pooled and subgroup analysis was estimated by fixed-effect model. If the heterogeneity was high ($I2 \geq 75\%$), we did not estimate an overall pooled effect.

Results

We identified 225 reviews through the database search with our search terms, of which 172 reviews were screened out during by title and abstract screening. 46 reviews were excluded after full-text assessment that were not systematic reviews, not within the past 5 years, not based on RCTs, or had no hand hygiene intervention or no laboratory-confirmed influenza outcome. In total, seven reviews were included in our analysis, from which we identified nine eligible articles. The most recent systematic review and meta-analysis was published in 2014; it reviewed and analysed RCTs to study the effect of hand hygiene on the prevention of laboratory-confirmed influenza (*15*). The process of identifying these review articles is shown in Fig. 2.

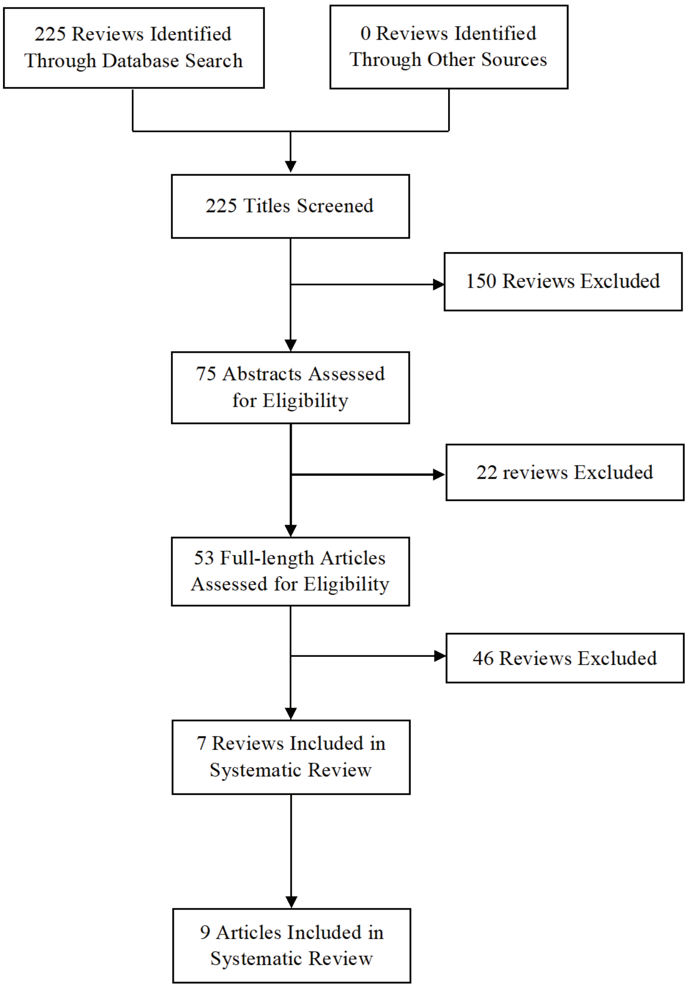


Fig. 2. The flow chart of hand hygiene review selection

In the additional search to update the systematic review by Wong et al. (*15*) that was published in 2014, 352 articles were identified from 1 January 2013 to 14 August 2018. At total of 319 articles were excluded in the title and abstract screening. 30 articles were excluded that were not RCTs, not done outside of health care settings, did not have a hand hygiene intervention or did not have a laboratory-confirmed influenza outcome. Three additional articles were identified since the publication of the review by Wong et al. (*15*). In total, 12 articles (11 studies; Azman et al. (*16*) and Stebbins et al. (*17*) were the same project during the same period but studied different questions) were included in our systematic review and 11 articles (10 studies; Levy et al. (*18*) only had household level secondary infection data but no individual level data) were included in the meta-analysis. The article selection flow is shown in Fig. 2.

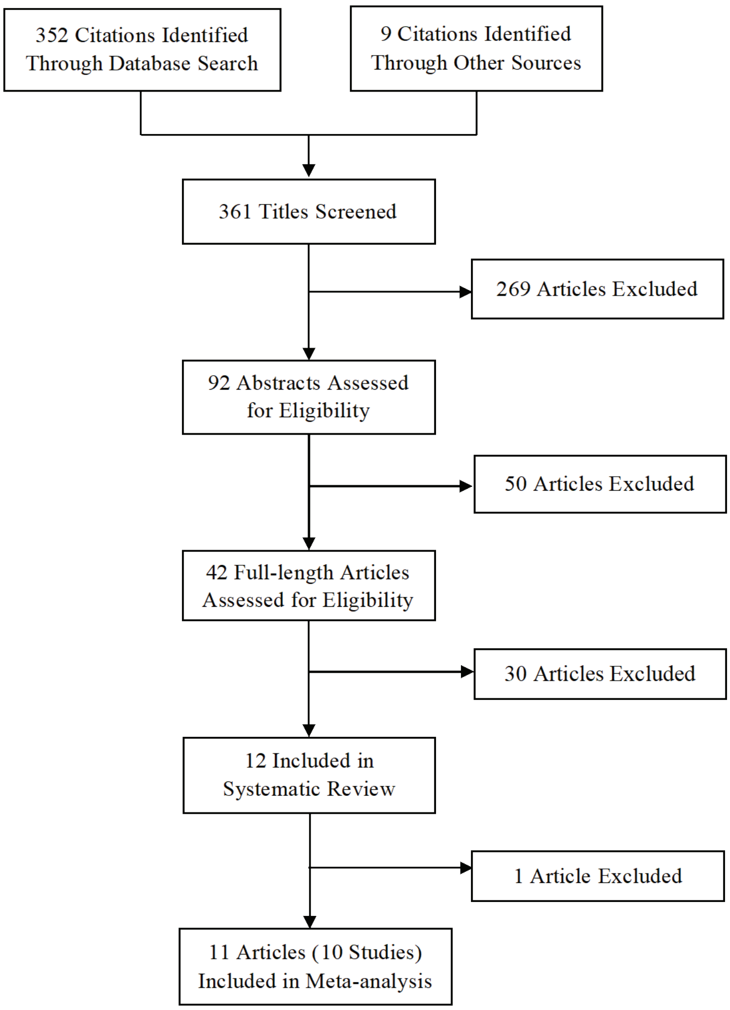


Fig. 3. The flow chart of hand hygiene article selection

Table 2. Basic characteristics of included studies

CHARACTERISTICS	NO. OF STUDIES (%)
Country	
Developed	7 (64)
Developing	4 (36)
Setting	
Household	7 (64)
Elementary school	2 (18)
University residential hall	2 (18)
Transmission mode	
Primary	5 (45)
Secondary	6 (55)
Intervention evaluated[a]	
Hand sanitizer and education	3 (20)
Hand sanitizer, soap and education	1 (7)
Hand sanitizer and face mask	3 (20)
Hand sanitizer, face mask and education	2 (13)
Soap	3 (20)
Soap and education	1 (7)
Soap and face mask	2 (13)
Outcome assessed	
Laboratory-confirmed influenza	11 (100)

[a] More than one intervention for some studies.

Among the 11 included studies, 7 studies were in household settings, two in elementary schools and two in university residential halls. Included study information is shown in Table 2, and detailed study description and evidence quality assessment are shown in Table 3. The evidence profile for the outcomes is summarized in Table 4.

In the pooled analysis, hand hygiene with face mask (RR = 0.91, 95% CI: 0.73–1.13, p = 0.39, I2 = 35%) did not have a statistically significant protective effect in non-health care settings (Fig. 4) *(19-24)*. Some published studies noted that poor adherence to hand hygiene may lead to underestimation of the true effect of the intervention (*19, 21, 22*).

The relative importance of transmission modes of influenza may vary in different settings. In school settings, no total effect was generated due to high heterogeneity (Fig. 5) (*17, 25*). In a study in the United States of America (USA), there was no significant effect of hand hygiene with a point estimate of the risk ratio close to 1, whereas a large trial in Egypt reported a reduction of more than 50% in influenza cases in the intervention group.

Hand hygiene with face mask intervention contributed to 52% relative risk reduction (RR = 0.48, 95% CI: 0.21–1.08, p = 0.08, marginally significant, I2 = 0%) of laboratory-confirmed influenza infection in university residential hall (Fig. 6) (*20, 23*).

The efficacy of hand hygiene with or without face mask was insignificant (RR = 1.05, 95% CI: 0.86–1.27, p = 0.65, I2 = 57%) in household setting in the analysis (Fig. 7) (*19, 21, 22, 24, 26, 27*). Although the pooled analysis did not identify a significant effect of hand hygiene overall, some household transmission studies reported that implementing hand hygiene intervention earlier after onset in the index case might be more effective in preventing secondary cases in the household (*19, 24*).

Experimental studies found that influenza virus could not survive long on human hands (*28, 29*). Viable influenza virus could be transmitted from contaminated surfaces to human hands by rubbing (*30*). Simmerman cultured live influenza virus from a finger swab sample from a laboratory-confirmed influenza patient (*31*). This evidence suggested the biological plausibility of indirect contact transmission via contaminated hands of influenza. Experimental studies also claimed that hand hygiene practice (e.g. handwashing with water and soap, and handrubbing with alcohol-based handrub) is effective to inactivate or reduce viable influenza virus on human hands (*32-34*). These results highlighted the importance of hand hygiene and suggested that hand hygiene may be initiative to prevent influenza transmission.

Ethical considerations

There are no major ethical issues. Alcohol-based handrub might be not available in some locations due to religious objections, such as the situation of incompliance of hand hygiene recommendation among Muslim health care workers (35). Skin irritation by alcohol handrub is possible, although the irritant potential of alcohol-based handrub is very low (*36*). Low adherence to hand hygiene intervention was observed in some studies (*19, 21, 22, 26*).

Knowledge gaps

Our review identified 10 RCTs of hand hygiene against laboratory-confirmed influenza. The pooled estimate of the effectiveness of hand hygiene in household settings was close to the null, with a fairly narrow confidence interval (Fig. 7), and future studies are unlikely to move the pooled estimate far from the null even if individual trials done in the future show protective efficacy of hand hygiene. In schools, there are only two published trials, and there is a clear need for additional studies to resolve the discrepancy between those two studies from the USA and Egypt (*17, 25*), one of which showed a considerable effect of hand hygiene (Fig. 5).

A more basic knowledge gap is on mechanisms of person-to-person transmission of influenza, including virus survival on hands and different types of surfaces, and the potential for contact transmission to occur in different locations and with different environmental conditions. Randomized trials of hand hygiene can contribute to determining modes of influenza transmission because hand hygiene would primarily act against one specific mode of transmission (indirect contact) but not other modes (respiratory droplets of varying sizes) (*37*).

Table 3. Description of studies included in the review of hand hygiene

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Azman AS, 2013 (*16*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary and secondary	Hand sanitizer, soap and education	The primary transmission outcome refers to Stebbins, S. 2011; no significant difference in secondary ILI attack rate between intervention group and control group	Moderate
Levy JW, 2014 (*18*)	Cluster-RCT Household level	2009–2010	191 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Less secondary influenza infections in households in the intervention group than control group, but not statistically significant; handwashing reduces surface influenza RNA contamination	Moderate
Ram PK, 2015 (*27*)	Cluster-RCT Household level	2009–2010	384 households with index case-patients recruited from a hospital in Kishoregoni, Bangladesh	Secondary	Handwashing with soap and education	Handwashing promotion did not prevent secondary influenza infection in household setting	Moderate
Aiello AE, 2010 (*20*)	Cluster-RCT University residence hall level	2006–2007 influenza season	1297 participants recruited from7 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	The laboratory-confirmed influenza protective effect of intervention is not significant; but the intervention is significant in ILI reduction	Moderate
Aiello AE, 2012 (*23*)	Cluster-RCT University residence hall level	2007–2008 influenza season	1111 participants recruited from 5 residential halls in Michigan, USA	Primary	Hand sanitizer and face mask; face mask	Reductions in the rates of influenza in the intervention groups, but not significant; significant reduction in the rates of ILI	High
Cowling BJ, 2008 (*26*)	Cluster-RCT Household level	2007	198 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; face mask and education	No significant difference between intervention groups and control group in laboratory-confirmed influenza and clinical secondary attack rate	Moderate

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	TRANSMISSION MODE	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Cowling BJ, 2009 (*19*)	Cluster-RCT Household level	2008	259 households with index subjects recruited from outpatient clinics in Hong Kong SAR, China	Secondary	Hand sanitizer and education; hand sanitizer, face mask and education	Hand hygiene and face mask intervention prevent influenza transmission, but not statistically significant; among the households implementing interventions within 36 hours symptom onset of index cases, the interventions significantly reduce influenza transmission	Moderate
Larson EL, 2010 (*21*)	Cluster-RCT Household level	2006–2008	509 households were recruited in New York, USA	Primary	Hand sanitizer and education; hand sanitizer, face mask and education	There is no detectable benefit of hand hygiene, face mask and education intervention on influenza prevention	Moderate
Simmerman JM, 2011 (*22*)	Cluster-RCT Household level	2008–2009	442 households with index children recruited from a public paediatric hospital in Bangkok, Thailand	Secondary	Handwashing; handwashing and face mask	Hand hygiene and face mask intervention did not reduce influenza transmission	Moderate
Stebbins S, 2011 (*17*)	Cluster-RCT School level	2007–2008 influenza season	3360 students from 10 elementary schools in Pittsburgh, USA	Primary	Hand sanitizer, soap and education	"WHACK the Flu" programme did not reduce laboratory-confirmed influenza infection, but reduced absence episodes and laboratory-confirmed influenza A	Moderate
Suess T, 2011 (*24*)	Cluster-RCT Household level	2009–2010 pandemic season 2010–2011 influenza season	84 households with one influenza positive index case were recruited by general practitioners or paediatricians in Berlin, Germany	Secondary	Hand sanitizer and face mask; face mask	The interventions could reduce influenza transmission in household setting when implemented early and use properly	Moderate
Talaat M, 2011 (*25*)	Cluster-RCT School level	2008	44 451 students were enrolled from 60 elementary schools in Cairo, Egypt	Primary	Handwashing	Hand hygiene campaign effectively reduced different kinds of infectious disease, including laboratory-confirmed influenza	Moderate

ILI: influenza-like illness; RCT: randomized controlled trial; RNA: ribonucleic acid; SAR: Special Administrative Region; USA: United States of America.

Table 4. Grade evidence profile for hand hygiene

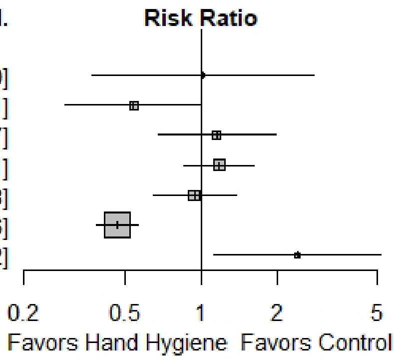
QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand hygiene with or without face mask versus control		Risk ratio	Quality	Importance
Effect of hand hygiene intervention on prevention of laboratory-confirmed influenza											
10	Randomized trial [1]	No serious risk of bias [2,3,4]	Serious [5]	No serious indirectness [6]	Serious [7]	Strong association [8]	434/6442 (6.7%)	504/5392 (9.3%)	Risk ratio cannot be generated because of high heterogeneity	Moderate	Important

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household, school and university residence level.
3 Five studies reported blinding of study staff including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded due to the nature of the study design.
4 Allocation concealment was adequate in all trials. Three studies used block randomization and seven studies used simple randomization.
5 High heterogeneity was observed in the pooled analysis (I2 > 50%).
6 Laboratory-confirmed influenza was the outcome for all studies.
7 Cowling B.J. 2008 and Suess T. 2011 reported insufficient number of participants. Cowling B.J. 2009 reported insufficient statistical power. Larson E.L. 2010 reported lower rate of illness was found compared to initial assumption. Simmerman J.M. 2011 reported did not reach the recruitment target. Talaat M. 2011 reported low rate of testing of students who were absent due to ILI.
8 Aiello AE (2012), rated as high-quality study, showed a large effect in favouring hand hygiene intervention – RR = 0.4.

Hand hygiene only

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2008)	5	84	12	205	1.5%	1.02	[0.37; 2.80]
Cowling (2009)	14	257	28	279	5.9%	0.54	[0.29; 1.01]
Larson (2010)	29	946	24	904	5.4%	1.15	[0.68; 1.97]
Simmerman (2011)	66	292	58	302	12.6%	1.18	[0.86; 1.61]
Stebbins (2011)	51	1695	53	1665	11.8%	0.95	[0.65; 1.38]
Talaat (2011)	125	808	281	848	60.8%	0.47	[0.39; 0.56]
Ram (2015)	17	177	10	250	1.8%	2.40	[1.13; 5.12]

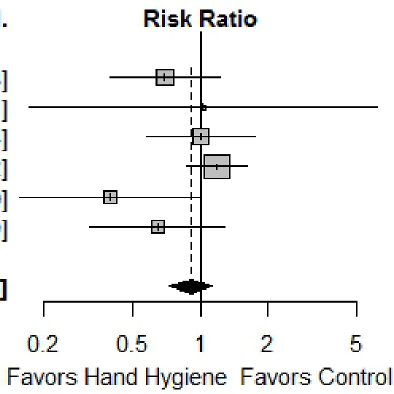
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.2837$, $p < 0.01$



Hand hygiene and facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2009)	18	258	28	279	18.8%	0.70	[0.39; 1.23]
Aiello (2010)	2	316	3	487	1.6%	1.03	[0.17; 6.11]
Larson (2010)	25	938	24	904	17.1%	1.00	[0.58; 1.74]
Simmerman (2011)	66	291	58	302	39.7%	1.18	[0.86; 1.62]
Aiello (2012)	6	349	16	370	10.8%	0.40	[0.16; 1.00]
Suess (2012)	10	67	19	82	11.9%	0.64	[0.32; 1.29]
Fixed effect model		**2219**		**2424**	**100.0%**	**0.91**	**[0.73; 1.13]**

Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.0511$, $p = 0.17$
Test for overall effect: $z = -0.85$ ($p = 0.39$)



Hand hygiene with or without facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2008)	5	84	12	205	1.3%	1.02	[0.37; 2.80]
Cowling (2009)	32	515	28	279	6.9%	0.62	[0.38; 1.01]
Aiello (2010)	2	316	3	487	0.5%	1.03	[0.17; 6.11]
Larson (2010)	54	1884	24	904	6.2%	1.08	[0.67; 1.73]
Simmerman (2011)	132	583	58	302	14.6%	1.18	[0.89; 1.55]
Stebbins (2011)	51	1695	53	1665	10.2%	0.95	[0.65; 1.38]
Talaat (2011)	125	808	281	848	52.4%	0.47	[0.39; 0.56]
Aiello (2012)	6	349	16	370	3.0%	0.40	[0.16; 1.00]
Suess (2012)	10	67	19	82	3.3%	0.64	[0.32; 1.29]
Ram (2015)	17	177	10	250	1.6%	2.40	[1.13; 5.12]

Heterogeneity: $I^2 = 82\%$, $\tau^2 = 0.2286$, $p < 0.01$

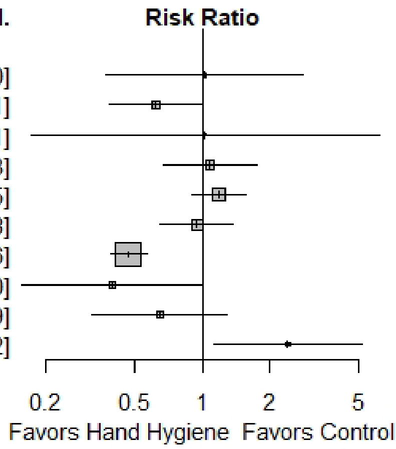


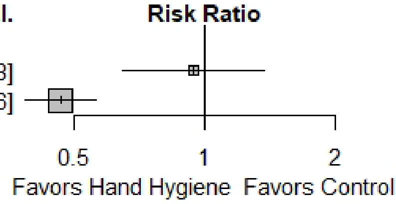
Fig. 4. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza (pooled analysis)

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥75%).

Hand hygiene only

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Stebbins (2011)	51	1695	53	1665	16.3%	0.95	[0.65; 1.38]
Talaat (2011)	125	808	281	848	83.7%	0.47	[0.39; 0.56]

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.2264$, $p < 0.01$



Hand hygiene with or without facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Stebbins (2011)	51	1695	53	1665	16.3%	0.95	[0.65; 1.38]
Talaat (2011)	125	808	281	848	83.7%	0.47	[0.39; 0.56]

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.2264$, $p < 0.01$

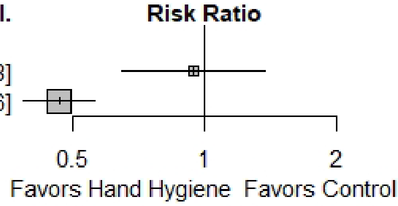


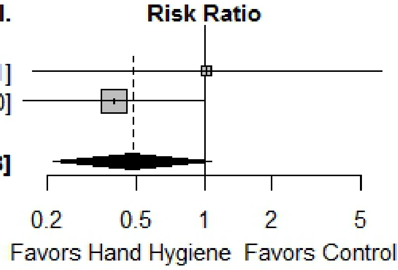
Fig. 5. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in elementary school setting

Note: Total effect would not be estimated when heterogeneity is high (I2 ≥ 75%).

Hand hygiene and facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Aiello (2010)	2	316	3	487	13.2%	1.03	[0.17; 6.11]
Aiello (2012)	6	349	16	370	86.8%	0.40	[0.16; 1.00]
Fixed effect model		**665**		**857**	**100.0%**	**0.48**	**[0.21; 1.08]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.35$
Test for overall effect: $z = -1.78$ ($p = 0.08$)



Hand hygiene with or without facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Aiello (2010)	2	316	3	487	13.2%	1.03	[0.17; 6.11]
Aiello (2012)	6	349	16	370	86.8%	0.40	[0.16; 1.00]
Fixed effect model		**665**		**857**	**100.0%**	**0.48**	**[0.21; 1.08]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.35$
Test for overall effect: $z = -1.78$ ($p = 0.08$)

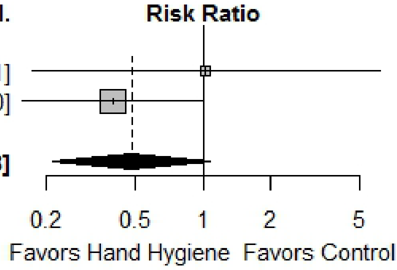
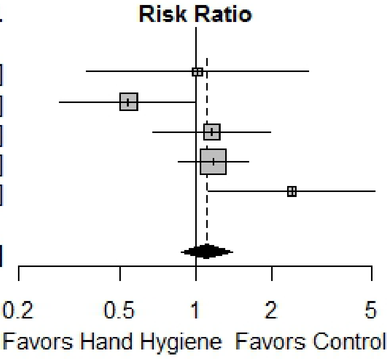


Fig. 6. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in university residential hall setting

Hand hygiene only

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2008)	5	84	12	205	5.6%	1.02	[0.37; 2.80]
Cowling (2009)	14	257	28	279	21.7%	0.54	[0.29; 1.01]
Larson (2010)	29	946	24	904	19.8%	1.15	[0.68; 1.97]
Simmerman (2011)	66	292	58	302	46.1%	1.18	[0.86; 1.61]
Ram (2015)	17	177	10	250	6.7%	2.40	[1.13; 5.12]
Fixed effect model		**1756**		**1940**	**100.0%**	**1.11**	**[0.88; 1.39]**

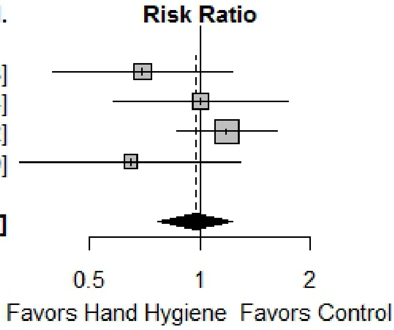
Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.1119$, $p = 0.05$
Test for overall effect: $z = 0.89$ ($p = 0.38$)



Hand hygiene and facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2009)	18	258	28	279	21.5%	0.70	[0.39; 1.23]
Larson (2010)	25	938	24	904	19.5%	1.00	[0.58; 1.74]
Simmerman (2011)	66	291	58	302	45.4%	1.18	[0.86; 1.62]
Suess (2012)	10	67	19	82	13.6%	0.64	[0.32; 1.29]
Fixed effect model		**1554**		**1567**	**100.0%**	**0.97**	**[0.77; 1.22]**

Heterogeneity: $I^2 = 28\%$, $\tau^2 = 0.0263$, $p = 0.24$
Test for overall effect: $z = -0.27$ ($p = 0.79$)



Hand hygiene with or without facemask

Author	Hand hygiene Events	Hand hygiene Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Cowling (2008)	5	84	12	205	3.9%	1.02	[0.37; 2.80]
Cowling (2009)	32	515	28	279	20.5%	0.62	[0.38; 1.01]
Larson (2010)	54	1884	24	904	18.3%	1.08	[0.67; 1.73]
Simmerman (2011)	132	583	58	302	43.0%	1.18	[0.89; 1.55]
Suess (2012)	10	67	19	82	9.6%	0.64	[0.32; 1.29]
Ram (2015)	17	177	10	250	4.7%	2.40	[1.13; 5.12]
Fixed effect model		**3310**		**2022**	**100.0%**	**1.05**	**[0.86; 1.27]**

Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.0950$, $p = 0.04$
Test for overall effect: $z = 0.46$ ($p = 0.65$)

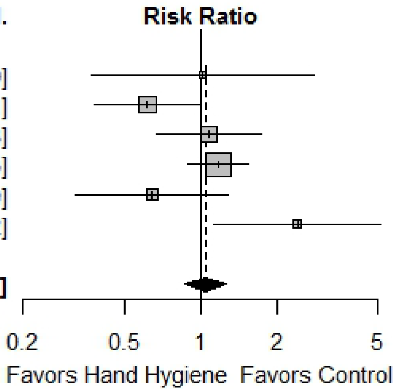


Fig. 7. Risk ratios for the effect of hand hygiene interventions with or without face mask on laboratory-confirmed influenza in household setting

1.2. Respiratory etiquette

Terminology

Definitions of respiratory etiquette are shown in Table 5.

Table 5. Definitions of respiratory etiquette terms

TERM	DEFINITION
Respiratory etiquette	Respiratory etiquette is also known as 'cough etiquette' (*38*). It is a simple hygiene practice to prevent person-to-person transmission of respiratory infections. Measures include (*39*): 1) Cover the mouth and nose with a tissue when coughing or sneezing 2) Find the nearest waste basket to dispose the used tissue immediately 3) Wash hands after touching respiratory secretions and/or contaminated objects

Methods

On 6 November 2018, we conducted a literature search in four databases: Medline (January 1946 to October 2018), PubMed (January 1950 to October 2018), EMBASE (1980 to October 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they investigated specifically the use of respiratory/ cough etiquette as the intervention along with the study outcome of laboratory-confirmed influenza virus infection. Studies that reported use of face mask as part of the respiratory etiquette were excluded because they will be covered in Section 1.3. Two independent reviewers (ES and SG) reviewed retrieved titles and subsequent relevant abstracts independently.

Results

A total of 80 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full-text articles were assessed for eligibility. No studies were identified for this review to quantify the efficacy of respiratory etiquette with the outcome of laboratory-confirmed influenza. The flow chart is shown Fig. 8.

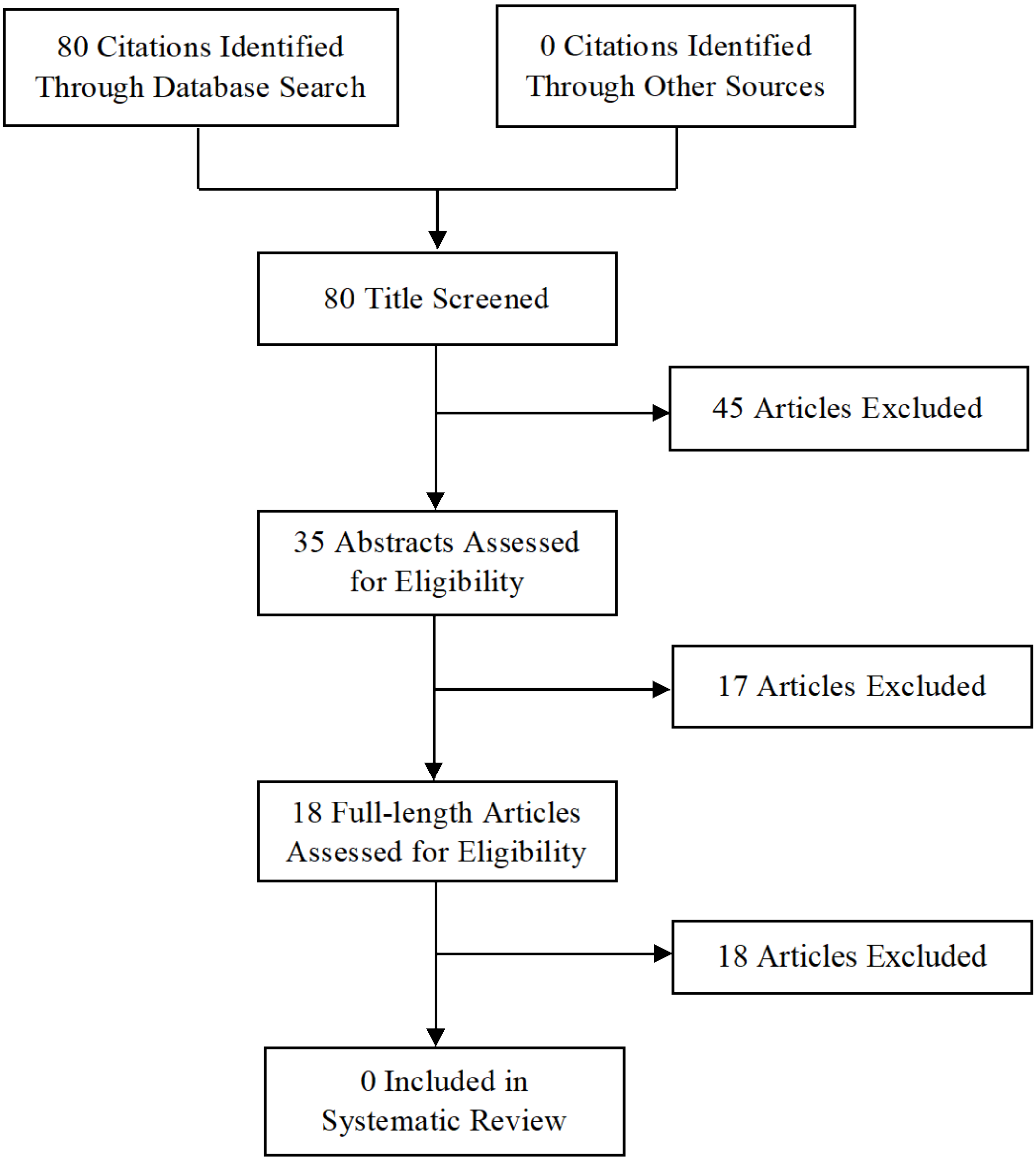


Fig. 8. Flow chart of the process and results of study selection

Balaban et al. reported a 2% reduction of self-reported respiratory illnesses, defined by one or more symptoms in cough, congestion, sore throat, sneezing or breathing problems, with the practice of cough etiquette among US pilgrims in the 2009 Hajj (*40*). Zayas et al. conducted an observational study to determine the effectiveness of respiratory etiquette manoeuvres in blocking the release of droplets or aerosols during coughing (*38*). They concluded the common respiratory etiquette (using surgical mask and hand, arm or sleeve, tissue) is not effective in blocking different diameter droplets to the surrounding environment and the majority of droplets dispersed to the environment when practicing the manoeuvre were < 1 µm.

Ethical considerations

No major ethical considerations. Cultural contexts may need to be considered when recommending specific actions such as covering coughs with hands or tissues.

Knowledge gaps

There is a need for further research in the best measures of respiratory etiquette for reducing influenza transmission (38).

1.3. Face masks

Terminology

Relevant terminology relating to face masks is shown in Table 6.

Table 6. Definitions of masks terms

TYPES OF MASKS	TERMINOLOGY
Clothing, scarf or rags tied over the nose and mouth	These are referred as alternative barriers to medical masks, but there is insufficient information available on their effectiveness *(41)*.
Cloth mask **Face mask**	Cloth masks can be referred to 'reusable masks made of cloth or any other fabric, including cotton, silk or muslin'(*42*) . Fitness of fabric and number of layers of a cloth mask determine its filtration capacity (*42*). Cloth masks should be cleaned thoroughly between each use (*43*). Washing with household detergent at normal temperature will be sufficient (*43*).
Respirator	A face mask, also known as surgical, isolation, dental or medical procedure masks, is a loose-fitting, disposable device that covers the mouth and nose of the user, and helps block large-particle droplets, splashes, sprays or splatter that may contain infectious agents (*44*). Face masks may also help reduce exposure of user's saliva and respiratory secretions to others (*44*). They may come with or without a face shield and are not designed to be shared (*44*). They are not designed to protect against breathing in small-particle aerosols that may contain viruses. Face masks should be used once and then disposed in the trash (*45*). Respirator, also known as filtering facepiece respirator, is a personal protective device that covers the nose and mouth of the user, and helps reduce the risk of inhaling hazardous airborne particles (including dust particles and infectious agents), gases, or vapours on the user (*46*). NIOSH in the USA certifies N, R and P series particulate filtering respirator types 95, 99 and 100 with minimum filtration efficiencies of 95, 99 and 99.97%, respectively. This certification is recognized by countries like Canada, Mexico and Chile. Several countries including Canada, Mexico and Chile. In Europe, respirators marked with 'Conformité Européen' (CE) such as FFP1 (class P1), FFP2 (class P2) and FFP3 (class P3) types meet minimum filtration efficiencies of 80, 94 and 99%, respectively (*47*). A label 'NIOSH' is required to be printed on the NIOSH-approved products with other information including part, lot number and company name; A label 'CE' on the product indicates EC conformity (*47*).

EC: European Community; NIOSH: National Institute for Occupational Safety and Health; USA: United States of America.

Methods

On 28 July 2018, we conducted a literature search in four databases: Medline (January 1946 to June 2018), PubMed (January 1950 to July 2018), EMBASE (1980 to June 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Articles of all languages were reviewed. Studies were selected if they were conducted in RCT in community settings such as households and schools, evaluated the use of face masks with or without the combination of other intervention as one intervention, and included the incidence of laboratory-confirmed influenza case as study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Qualities of studies were assessed by GRADE with an aim to evaluate the efficacy of community-based face mask use in the prevention of laboratory-confirmed influenza virus infections.

Results

A total of 1100 articles were retrieved from four electronic databases after removing duplicate records. Titles, abstract content and full text were subsequently reviewed for inclusion; 10 relevant studies were identified for this review and meta-analysis to quantify the efficacy of community based use of face masks after excluding 89 articles by full-text assessment. The flow chart is shown in Fig. 9. Of 10 studies, seven were conducted in household settings (*19, 21, 22, 24, 26, 48, 49*), with two studies conducted in university residence halls (*20, 23*), and one study conducted in Hajj pilgrims (*50*). Nearly half of the studies evaluated the effect of face mask use with the practice of handwashing, therefore results were analysed in two groups: comparison of control group with intervention group of face mask use only; and comparison of control group with intervention group of face mask use with or without handwashing.

Among the 10 selected studies, two studies by MacIntyre et al. had a slightly different study design. One study enrolled families in which one person had laboratory-confirmed influenza, and only required the household contacts to wear face masks or P2 masks (equivalent to a N95 respirator) (48), whereas the other study required only the ill members to wear face mask to evaluate the protective effect of face mask if worn by the ill individual (i.e. source control) (*49*). In the remaining eight studies, every participant in the face mask intervention group was supposed to wear a face mask.

MacIntyre et al. compared the protective effect of face mask and P2 mask but found no significant difference in influenza-like illness (ILI) and laboratory-confirmed respiratory infections (influenza A and B virus, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], adenovirus, human parainfluenza virus [PIV], coronavirus, rhinovirus, enterovirus or picornovirus); however, they reported a significant reduction in ILI if the mask was worn with good compliance in a secondary analysis (*48*).

Two studies by Aiello et al. were conducted in residence hall settings (*20, 23*). They randomized university residents by cluster (each residential hall forming a cluster unit) to face masks, enhanced hand hygiene, or both. They then measured the incidence of laboratory-confirmed influenza in students in each hall. The authors reported no significant difference in ILI and laboratory-confirmed influenza in these three randomized groups; however, they observed a significant reduction in ILI in the combined face mask and hand hygiene intervention group during the latter half of the study period in a secondary analysis.

Seven studies were conducted in household settings where a person with laboratory-confirmed influenza was recruited as a household index case, and the rate of secondary infections in the education group (control), mask group and/or hand hygiene group was monitored for illnesses and infections. All studies found no significant differences in the rate of laboratory-confirmed influenza virus infections in contacts in the face mask arms, and some studies reported that low compliance of the use of NPIs could affect the results (*21*). One study reported a significant reduction in laboratory-confirmed influenza virus infections in contacts in the face mask and hand hygiene group in the subset of households where the intervention was applied within 36 hours of symptom onset in the index case (*24*).

Ten studies were pooled to conduct a meta-analysis to quantify the efficacy of community based use of face masks in the reduction of laboratory-confirmed influenza virus infection (Table 7). In the pooled analysis, there was a non-significant relative risk reduction of 22% (RR = 0.78, 95% CI: 0.51–1.20, I2 = 30%, p = 0.25) in the face mask group and 8% in the face mask group regardless of the addition of practice of hand hygiene (RR = 0.92, 95% CI: 0.75–1.12, I2 = 30%, p = 0.40). The evidence profile for face masks outcome is summarized in Table 8.

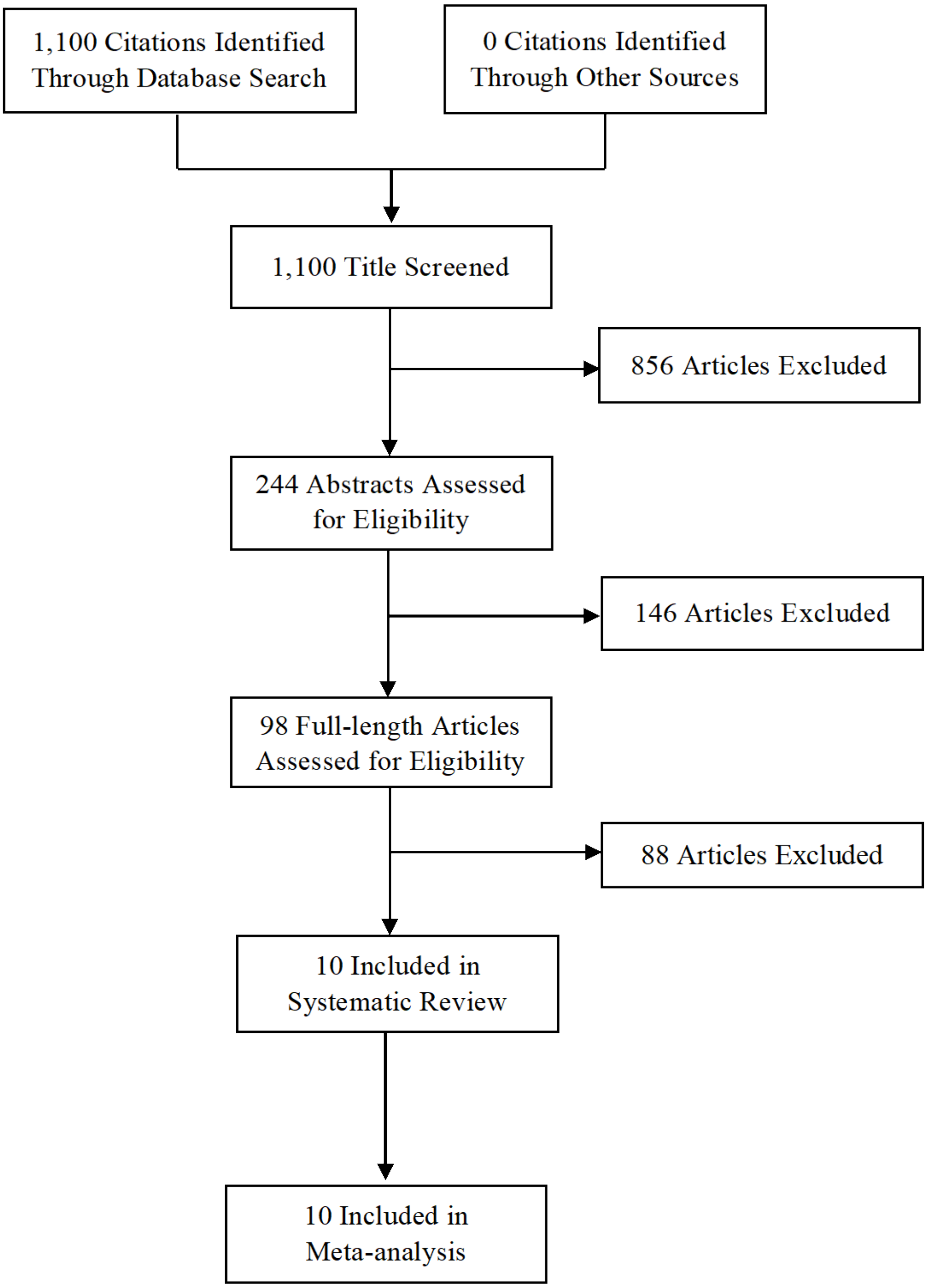
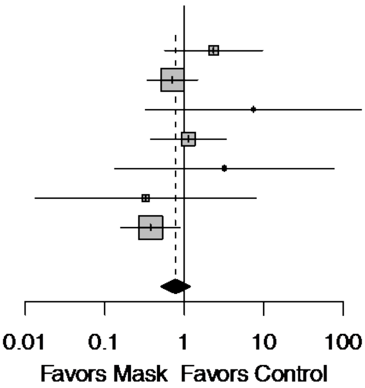


Fig. 9. The flow chart of the process and results of study selection

Mask only

Author	Mask use Events	Mask use Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Aiello (2010)	5	347	3	487	5.7%	2.34	[0.56; 9.72]
Aiello (2012)	12	392	16	370	37.3%	0.71	[0.34; 1.48]
Barasheed (2014)	1	11	0	28	0.7%	7.43	[0.33; 169.47]
Cowling (2008)	4	61	12	205	12.5%	1.12	[0.37; 3.35]
MacIntyre (2009)	1	94	0	100	1.1%	3.19	[0.13; 77.36]
MacIntyre (2016)	0	302	1	295	3.4%	0.33	[0.01; 7.96]
Suess (2012)	6	69	19	82	39.4%	0.38	[0.16; 0.89]
Fixed effect model		**1276**		**1567**	**100.0%**	**0.78**	**[0.51; 1.20]**

Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.1899$, $p = 0.20$
Test for overall effect: $z = -1.15$ ($p = 0.25$)



Mask with or without hand hygiene

Author	Mask use Events	Mask use Total	Control Events	Control Total	Weight	Risk Ratio	95% C.I.
Aiello (2010)	7	663	3	487	2.1%	1.71	[0.45; 6.59]
Aiello (2012)	18	741	16	370	13.0%	0.56	[0.29; 1.09]
Barasheed (2014)	1	11	0	28	0.2%	7.43	[0.33; 169.47]
Cowling (2009)	18	258	28	279	16.3%	0.70	[0.39; 1.23]
Cowling (2008)	4	61	12	205	3.3%	1.12	[0.37; 3.35]
Larson (2010)	25	938	24	904	14.9%	1.00	[0.58; 1.74]
MacIntyre (2009)	1	94	0	100	0.3%	3.19	[0.13; 77.36]
MacIntyre (2016)	0	302	1	295	0.9%	0.33	[0.01; 7.96]
Simmerman (2011)	66	291	58	302	34.6%	1.18	[0.86; 1.62]
Suess (2012)	16	136	19	82	14.4%	0.51	[0.28; 0.93]
Fixed effect model		**3495**		**3052**	**100.0%**	**0.92**	**[0.75; 1.12]**

Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.0593$, $p = 0.17$
Test for overall effect: $z = -0.84$ ($p = 0.40$)

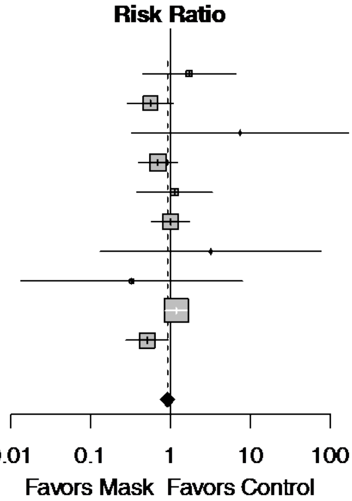


Fig. 10. Effects of face mask use interventions with or without enhanced hand hygiene on laboratory-confirmed influenza in 10 studies

Ethical considerations

No major ethical considerations. Masks may be more culturally acceptable in some locations than others, and a variety of factors may affect compliance.

Knowledge gaps

In the studies of face mask use with or without hand hygiene, the pooled estimate of the risk reduction against laboratory-confirmed influenza was 0.90 (95% CI: 0.75–1.12), which suggests that additional randomized trials would be less likely to identify a substantial protective efficacy of face masks. However, the majority of these studies were conducted in households in which at least one person was infected, and exposure levels might be relatively higher. Additional studies of face mask use in the general community would be valuable. While respirators should provide better protection against respiratory infections compared to face masks because of their higher filtration efficiency, a household randomized controlled study showed no difference in their effect on ILIs and laboratory-confirmed influenza virus infection (*48*). One issue is that respirators require fit testing for optimal performance, but fit testing facilities are not widely available in the community.

Table 7. Description of studies included in the review of face masks

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME & FINDING	QUALITY OF EVIDENCE
Aiello AE, 2010 (20)	Cluster-randomized intervention trial	Nov 2006 – Mar 2007	1437 university hall residents (USA)	Mask; Mask + Hand hygiene; control	Significant reduction in ILI during weeks 4–6 in mask and hand hygiene group compared to control; No significant reduction in ILI in mask and hand group or mask-only group or control	Moderate
Aiello AE, 2012(*23*)	Cluster-randomized interventional trial	Nov 2007 – Mar 2008	1178 university hall residents (USA)	Mask; Mask + Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in mask and hand group or mask-only group or control group	Moderate
Barasheed O, 2014 (*50*)	Non-blinded cluster-randomized trial	Nov 2011 – Nov 2011	164 Australian pilgrims (Saudi Arabia)	Mask; control	No significant difference in laboratory-confirmed influenza in two arms; protective effect against syndromic ILI compared to controls (31% versus 53%, p = 0.04)	Moderate
Cowling BJ, 2008 (*26*)	Cluster-randomized intervention trial	Feb 2007 – Sep 2007	198 laboratory-confirmed influenza case and their household contacts	Mask; Hand hygiene; control	No significant reduction in the secondary influenza attack rate in control, mask or hand group	Moderate
Cowling BJ, 2009 (*19*)	Cluster-randomized intervention trial	Jan 2008 – Sep 2008	407 laboratory-confirmed influenza case and 794 household members	Mask; Mask + Hand hygiene; control	No significant difference in rates of laboratory-confirmed influenza in hand-only or mask and hand group	Moderate
Larson EL, 2010 (*21*)	Cluster-randomized intervention trial	Nov 2006 – Jul 2008	617 households	Mask + Hand hygiene; Hand hygiene; control	No significant reduction in rates of laboratory-confirmed influenza in control, hand, mask or hand group	Moderate
MacIntyre CR, 2009 (*48*)	Cluster-randomized intervention trial	Aug 2006 – Oct 2006 & Jun 2007 – Oct 2007	145 laboratory-confirmed influenza case and their adult household contacts	Surgical mask; P2 mask; control	No significant difference in rate of laboratory-confirmed influenza in control, face mask or P2 mask group	Moderate
MacIntyre CR, 2016 (*49*)	Cluster-randomized intervention trial	Nov 2013 – Jan 2014	245 ILI index case and 597 household contacts	Mask; control	Clinical respiratory illness, ILI and laboratory-confirmed viral infections were lower in the mask arm compared to control, but results were not statistically significant	Moderate
Simmerman JM, 2011) (*22*)	Cluster-randomized intervention trial	Apr 2008 – Aug 2009	465 laboratory-confirmed influenza case and their household contacts	Mask + Hand hygiene; hand hygiene; control	No significant reduction in rate of secondary influenza infection in control, hand, mask or hand group	Moderate
Suess (2012) (*24*)	Cluster-randomized intervention trial	Nov 2009 – Jan 2010 & Jan 2011 – Apr 2011	84 laboratory-confirmed influenza case and 218 household contacts	Mask; Mask + Hand; control	No significant difference in rate of laboratory-confirmed influenza in control, mask, mask or hand group	Moderate

ILI: influenza-like illness; USA: United States of America.

Table 8. Grade evidence profile for face masks

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mask	Control	Risk ratio	Quality	Importance
10	RCT [1,2]	No serious risk of bias [3,4]	No serious inconsistency [5]	No serious indirectness	Serious [6]	None	156/3495	161/3052	0.92 (0.75,1.12)	Moderate	Important

RCT: randomized controlled trial.

1 All studies were randomized trials.
2 All studies were cluster-RCTs at household and university residence level.
3 Eight studies reported blinding of study staffs including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded.
4 Three studies used block randomization; six studies used computer program to generate the randomization order and one study used ticket-picking for selection.
5 Moderate heterogeneity was observed in the pooled analysis.
6 Six studies did not have sufficient sample size in each intervention group; 3 studies reported insufficient statistical power; one study reported insufficient detection of influenza case.

2. ENVIRONMENTAL MEASURES

2.1. Surface and object cleaning

Methods
We conducted a systematic review on the effect of surface and object cleaning in preventing influenza virus infections in non-health care settings. PubMed, Medline, EMBASE and CENTRAL were searched for articles on 15 October 2018.

Study selection criteria were studies reporting the effect of surface and object cleaning intervention with no intervention in preventing influenza virus infections in community settings. RCTs and other types of epidemiological studies were included if they aimed to study the effect of surface and object cleaning on laboratory-confirmed influenza, ILI or respiratory illness. Simulation studies, recommendations, and commentaries or editorials were excluded. A community setting was defined as an open setting without confinement and special care for the patients. Articles describing any surface and object cleaning related interventions were included. No language limits were applied.

Two independent reviewers (ZX and ES) reviewed titles, abstracts and full texts. After confirmed included studies, data extraction and evidence quality assessment were performed by the reviewers. The GRADE framework was used to evaluate the effect of surface and object cleaning on influenza.

Results
There were 484 articles retrieved through database search. 462 articles were excluded through title and abstract screening. In the full-text assessment, 19 articles were screened out due to no surface and object cleaning intervention or no specific respiratory infection outcome. Finally, three articles were included in the systematic review to study the effectiveness of surface and object cleaning to prevent influenza infection. The article selection flow is shown in Fig. 11.

A cross-sectional study showed that bleach use in households was significantly associated with an increased in the rate of self-reported influenza (influenza data were obtained from self-administered questionnaires and the paper did not specify whether it was laboratory-confirmed influenza or ILI), and the authors hypothesized that this might due to the immunosuppressive properties of bleach (*51*). An RCT with disinfection of toys and linen in day care nurseries found a reduction in the detections of viruses in the environment, but no significant effect on influenza virus specifically and no significant reduction in acute respiratory illnesses among children (*52*). Another RCT conducted in elementary schools demonstrated that hand hygiene with alcohol-based hand sanitizer and surface disinfection with quaternary ammonium wipes intervention could reduce gastrointestinal illness absenteeism, but not respiratory illness absenteeism (*53*). Detailed data extraction is shown in Table 9 below.

Experimental studies found that laboratory-grown influenza virus could survive on common surfaces and objects (e.g. stainless steel, wood, plastic, cloth and banknotes) from community settings for a few hours and up to 1 week (*28, 30, 54-56*). Influenza virus RNA could be detected by polymerase chain reaction (PCR) on surfaces and objects in household, school and airport settings in the field studies (*31, 52, 57-60*). Killingley et al. found viable influenza virus in the environment with laboratory-confirmed influenza individuals (*59*). These results suggested the biological plausibility that influenza virus could transmit via the fomite route. And the results from some experimental studies showed that disinfection process with different disinfection products (e.g. ethanol and 1-propanol) was effective to inactivate or reduce infectious influenza virus on surfaces (*61-63*), which suggested the importance of surface and object cleaning in influenza transmission prevention.

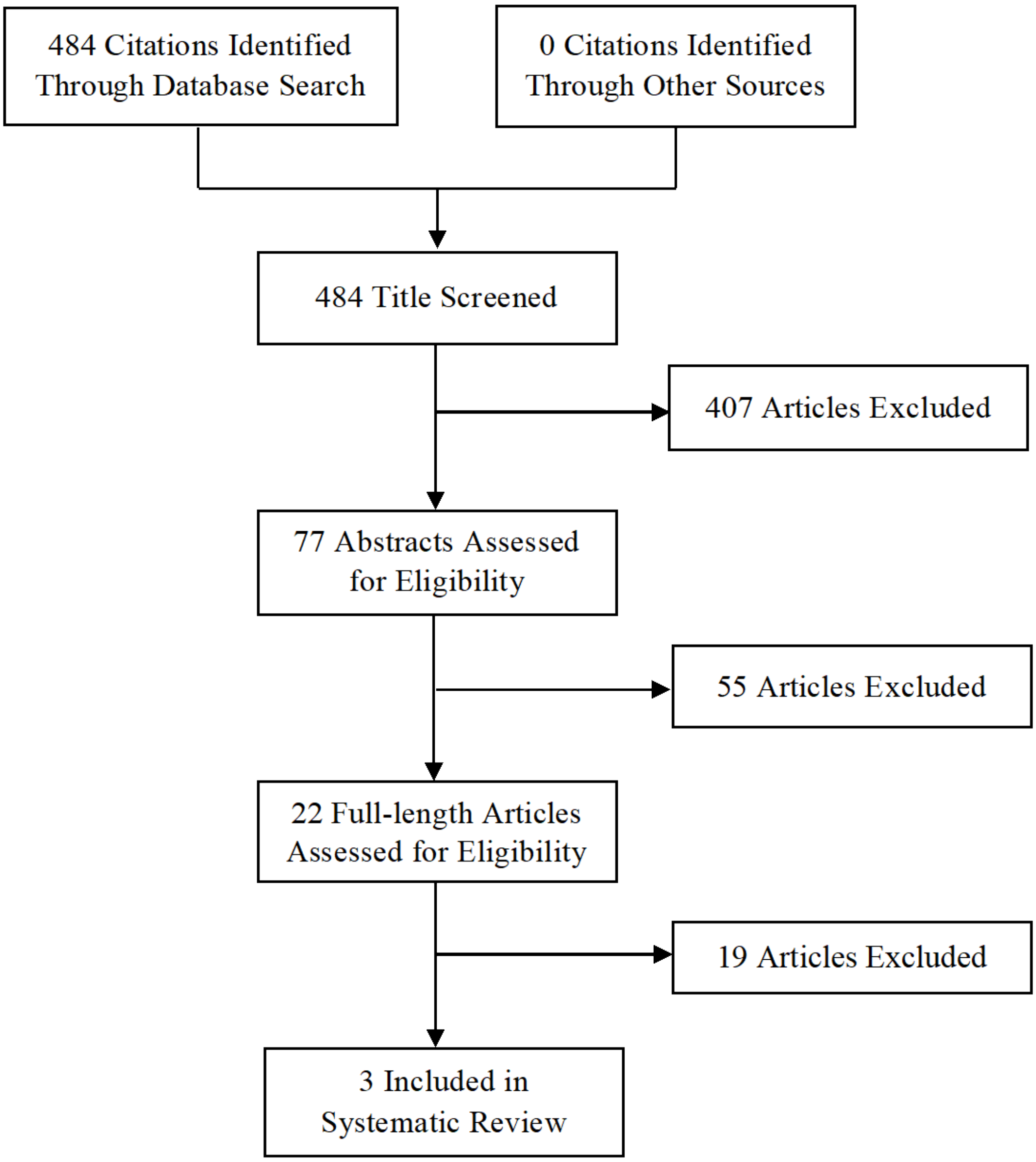


Fig. 11. The flow chart of surface and object cleaning articles selection

Ethical considerations

Disinfection product selection is a major issue, especially in public settings. Some disinfectants are irritants and may lead to adverse effect in sensitive population (*51*), and some disinfectants with alcohol may not be applicable in some countries or regions due to religious objections (*35*). In addition, the safety of cleaning personnel should also be considered. Proper training should be provided for the cleaning personnel, including proper use of the disinfectant (usage, dosage and time) and precautions before cleaning, such as wearing protective clothing.

Knowledge gaps

Only three studies were included in our systematic review and only two of them were RCTs. More trials are needed to study the effect of surface and object cleaning on influenza prevention. The best evidence for pandemic preparedness would be provided by studies in which the outcome is laboratory-confirmed influenza, rather than acute respiratory infections. Studies in various settings (e.g. household, school, workplace and public place) are also needed. The effect of different disinfection products to prevent influenza virus infection in terms of disinfection frequency, disinfection dosage, disinfection time point, and disinfection targeted surface and object material remained unknown.

Table 9. Description of studies included in the review of surface and object cleaning

STUDY	STUDY DESIGN	STUDY PERIOD	POPULATION & SETTING	INTERVENTION	OUTCOME MEASURE	MAIN FINDING	QUALITY OF EVIDENCE
Casas L, 2015 (*51*)	Cross-sectional study	2008–2010	9102 students from schools in Spain, Netherlands and Finland	Environment cleaning with bleach	Self-reported influenza	Passive contact with cleaning bleach in the household may increase the risk of respiratory and other infections in children, which may adversely affect the health of school-age children	Very low
Ibfelt T, 2015 (*52*)	Cluster-RCT	Autumn 2012 – April 2013	Twelve day-care nurseries (caring for 587 children) in Copenhagen, Denmark	Disinfection of toys	Respiratory infections and surface sample influenza virus detection	Frequently disinfection of toys could reduce environmental microbial presence, but not significantly reduce respiratory sickness of nursery children	Low
Sandora TJ, 2008 (*53*)	Cluster-RCT	March-May 2006	285 students from elementary schools in Avon, Ohio, USA	Hand hygiene and surface cleaning	Respiratory illness	Surface disinfection reduced gastrointestinal related absenteeism among school-age children, but not respiratory illness-related ones	Low

RCT: randomized controlled trial; USA: United States of America.

2.2. (*1*) Other environmental measures (UV light)

Terminology

The definition of ultraviolet (UV) light is shown in Table 10.

Table 10. Definition of UV light terms

TERM	DEFINITION
Ultraviolet light (UV light)	UV light is electromagnetic radiation that can be categorized into three groups by wavelength bands *(64)*: 1) UV-A (400–315 nm): It can be used for various purposes like pest control or identifying counterfeit banknotes. 2) UV-B (315–280 nm): It is known for the development of skin cancer. 3) UV-C (280–100 nm): It is used for disinfection of drinking water and sterilization of apparatus.
Ultraviolet germicidal irradiation (UVGI)	It is a mean of disinfection which breaks down microorganisms and can be used to prevent the spread of certain infectious diseases (*65*)

Methods

On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies were selected if they mentioned the use of UV light in community setting and reported laboratory-confirmed influenza virus infections as a study outcome. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results

A total of 1155 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 67 abstracts were selected for subsequently screening and eventually 39 full texts were assessed for eligibility. No studies were identified in this review to quantify the efficacy of UV light with the laboratory-confirmed influenza outcome. The flow chart is shown in Fig. 12.

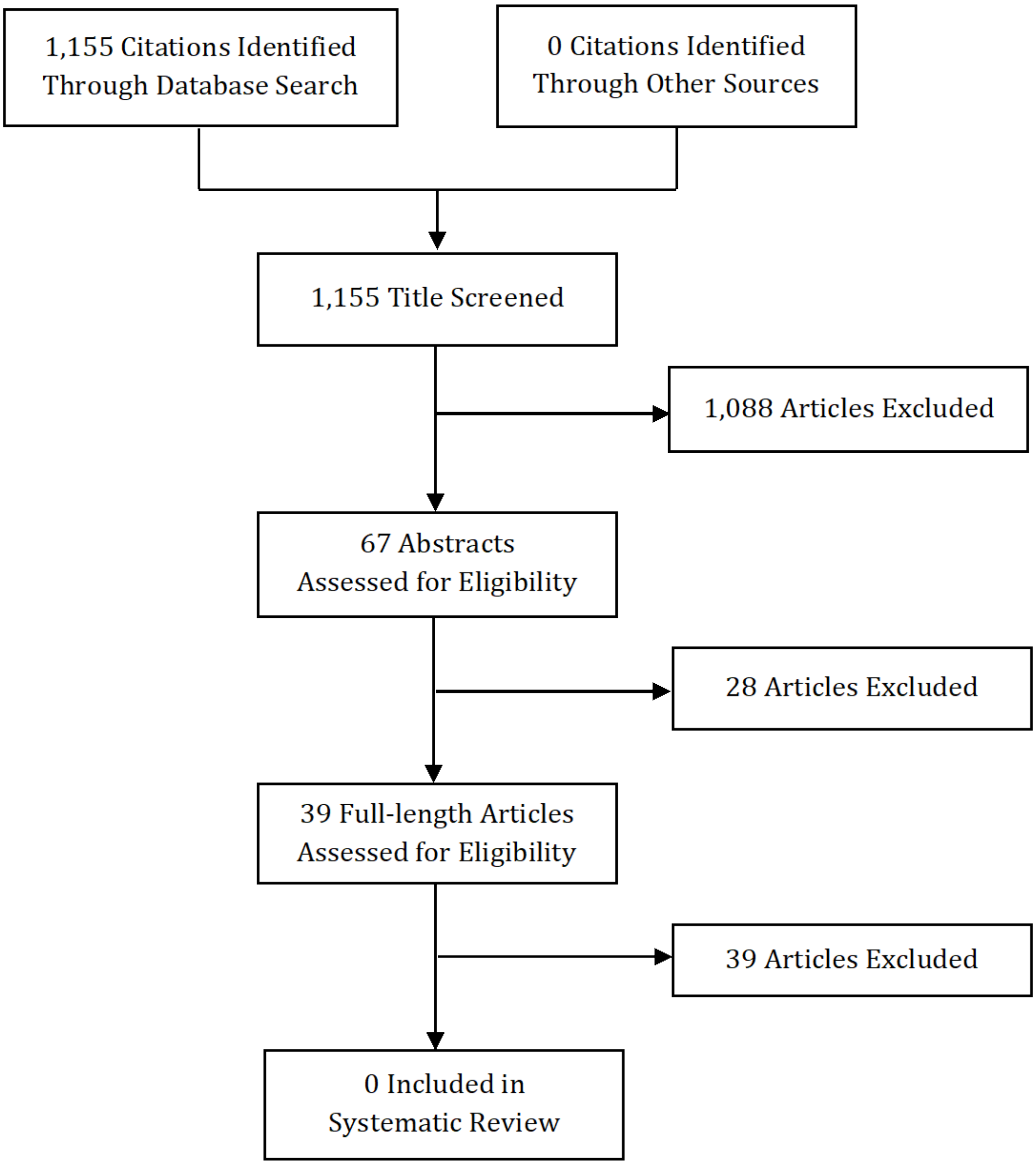


Fig. 12. The flow chart of the process and results of study selection

Ethical considerations

Exposure to UV light at certain wavelengths can increase the risk of skin cancer and cataracts; one study estimated that up to 20% of cataracts were due to UV overexposure (*64*). The use of UV light in occupied areas would need to be implemented carefully to control risks.

Knowledge gaps

The effectiveness of UV light in reducing the incidence of influenza virus infections still requires more evidence. Potential safety issues are also an important issue. Welch et al. reported that a low dose of far-UV-C light could inactivate aerosolized influenza H1N1 virus in a test chamber, and they reported an harmless effect on exposed mammalian skin (*66*), but more evidence is needed to confirm the impact of far-UV-C light in natural settings.

2.2. (2) Other environmental measures (ventilation)

Terminology
Definitions of ventilation are shown in Table 11 (*67*).

Table 11. Definition of ventilation terms

TERM	DEFINITION
Ventilation	Ventilation moves outdoor air into a building or a room, and distributes the air within the building.
Natural ventilation	Natural forces such as winds exchange the air in the building through windows, doors, solar chimneys, wind towers or trickle ventilators.
Mechanical ventilation	Mechanical ventilation uses mechanical fans to drive the outdoor air into the building at a designed flow rate.
	Mechanical ventilation can be integrated with air-conditioning system to control the indoor air temperature and humidity.
Hybrid (mixed-mode) ventilation	Combination of both mechanical and natural ventilation.
Air changes per hour (ACH)	The volume of air supplied to a room, in m3/hour, divided by the room volume, in m^3.

Methods
On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and CENTRAL (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that used modelling or simulation to describe the impact of ventilation on the rate of influenza virus infection in community settings were included. Two independent reviewers (ES and ZX) reviewed retrieved titles and subsequent relevant abstracts independently.

Results
A total of 630 articles were retrieved from four electronic databases after removing duplicate publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 35 abstracts were selected for screening and then 18 full texts were assessed for eligibility. Three studies were identified for this review to evaluate the contribution of ventilation in influenza infection in community settings, both from the same author. The flow chart is shown in Fig. 13. and the description for each study is shown in Table 12.

A stimulation study modelled the transmission potential levels in an elementary school and predicted a reduction of R0 (from 11.38 to 3.97) with an increase in air changes per hour (ACH) from 0.5 to 2 (*68*).

Another stimulation study on an influenza outbreak, with consideration of possible airborne transmission in a community predicted a 40% reduction of peak daily-infected ratio by increasing the ventilation from 1 ACH to 9 ACH, and the peak would delay from Day 30 to Day 240 by increasing the ventilation from 1 ACH to 7 ACH (*69*). The authors further predicted that the overall attack rate during an epidemic would reduce from 100% to 3.3% if the ACH increased from 1 to 7. They further studied the effectiveness of ventilation in another study, and predicted that doubling or tripling the ventilation rate could reduce the peak infection rate by over 60% under the assumption of equal contribution of airborne and close contact transmission; the authors concluded that an overall 30% reduction of peak infections was possible, even if airborne transmission only contributed to 20% of total infections (*70*).

Ethical considerations
No major ethical considerations.

Knowledge gaps
Mathematical models can only provide an indication of the potential spread of respiratory infections, and results can vary depending on the model assumptions. Experimental studies such as RCTs would provide more compelling evidence on the efficacy of increasing ventilation in reducing influenza transmission.

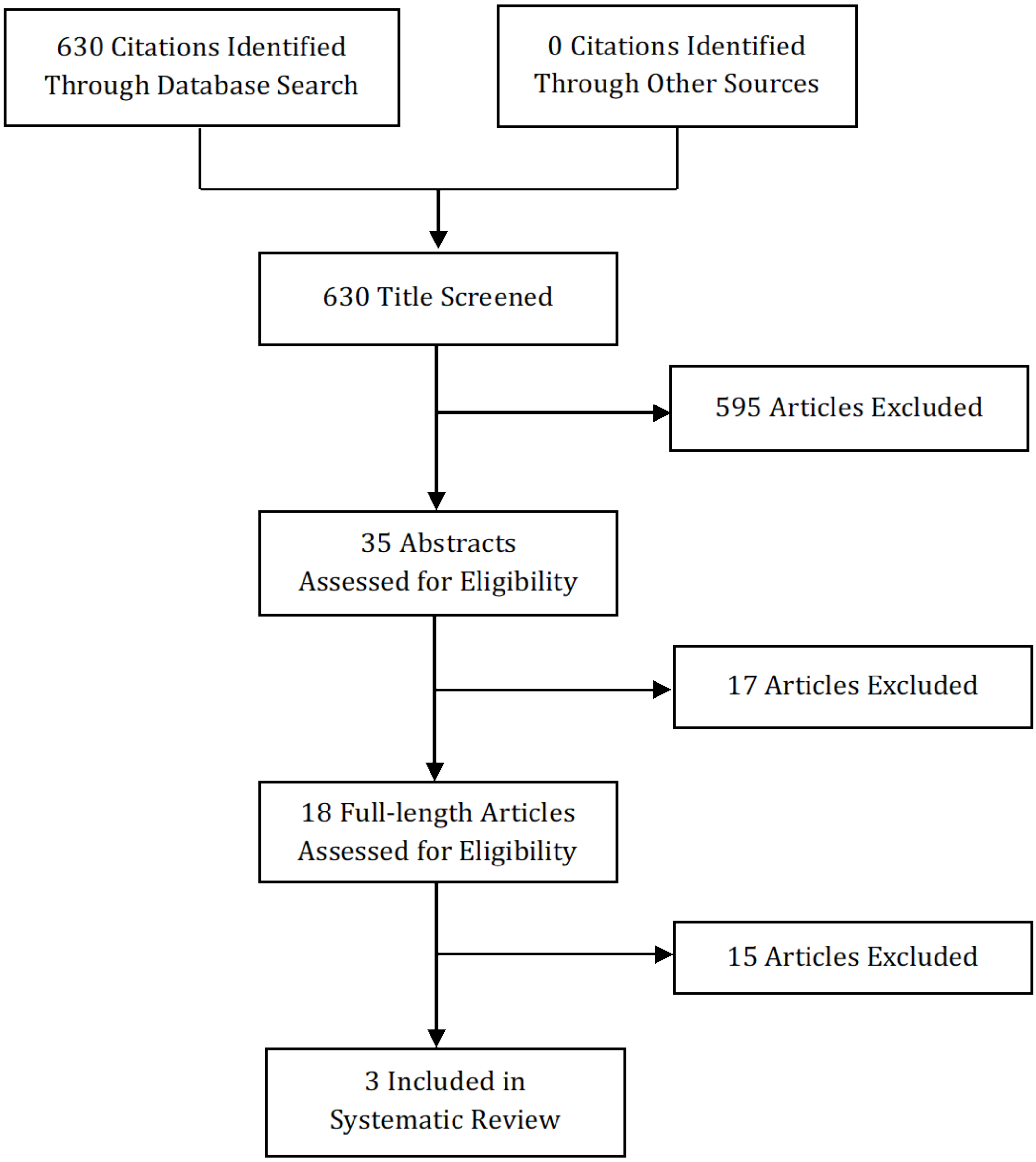


Fig. 13. The flow chart of the process and results of study selection

Table 12. Description of simulation studies included in the review of ventilation

STUDY	STUDY POPULATION	STUDY DESIGN	INTERVENTION	OUTCOME
Chen S, 2007 (*68*)	494 students (60 kindergarten and 434 elementary students) in an elementary school in Taipei City, Taiwan	Mathematical modelling	ACH, ACH + mask, 80% vaccination rate + 80% mask + 1.5 ACH	R0 is estimated to reduce from 11.38 to 3.97 for enhanced 0.5 and 2 ACH
Gao XL, 2009 (*69*)	Hong Kong SAR data in 2007	Mathematical modelling at community level	ACH, ACH + mask, ACH + UVGI, ACH + HEPA filter	Peak daily-infected ratio was reduced from 43% at 1 ACH to 21% at 3 ACH, 10% at 5 ACH, 3% at 7 ACH and 0.2% at 9 ACH; when ACH were increased from 1 to 5 ACH and 7 ACH, the disease attack rate was reduced from 100% to 69.8% and 3.3% respectively
Gao X, 2016 (*70*)	8 population groups (home stayers, office workers, classroom attendees, food service workers, shop workers, drivers, public space workers and other)	Mathematical modelling at 7 locations in communities	Ventilation, Ventilation + mask	Increasing ACH by doubling or tripling could reduce the peak infection rate by 65% and 83%; peak infection rate could reduce by about 34%, and outbreak could be delayed by over 50 days if applying a higher ventilation rate and masks for ill person

ACH: air changes per hour; HEPA: high-efficiency particulate air; R0: basic reproductive number; SAR: Special Administrative Region; UVGI: ultraviolet germicidal irradiation.

2.2. (*3*) Other environmental measures (humidity)

Terminology
Definitions of humidity are shown in Table 13.

Table 13. The definition of humidity terms

TERMS	TERMINOLOGY
Absolute humidity	A measure of actual amount of water vapour in the air, regardless of the air's temperature (expressed as grams of water per cubic metre volume of air) (*71*)
Relative humidity	A measure of amount of water vapour but relative to the temperature of air (expressed as a percentage) (*71*)

Methods

On 25 September 2018, we conducted a literature search in four databases: Medline (January 1946 to September 2018), PubMed (January 1950 to September 2018), EMBASE (1980 to September 2018), and Cochrane Library databases and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2018, Issue 5). Articles of all languages were included. Reference lists of retrieved articles were also reviewed for additional potential articles for this review. Studies that evaluated the impact of humidification in respect to the reduction of number of infected individuals in community settings were included.

Results

A total of 631 articles were retrieved from four electronic databases after removing duplicated publications. Titles, abstract content and full text were subsequently reviewed for inclusion; 16 abstracts were selected for subsequent screening, and eventually three full texts were assessed for eligibility. No studies were identified in Fig. 14.

Reiman et al. studied the effect of elevated humidification on influenza virus survival in preschool classrooms with the outcome measure being the detection of influenza virus in air and fomites *(72*). They reported a significant reduction of influenza A virus in air and on fomite (markers and wooden toys) in humidified preschool classrooms compared to control rooms. Detection rate of influenza A virus in air and fomites were 20% at humidified rooms (humidification maintained at 9.89 millibar) compared to 14.5% at control rooms (at 6.33millibar); the differences in influenza detection were statistically significant in both air and fomites. Myatt et al. simulated the airborne survival of influenza virus with the impacts of home humidification with the CONTAM a multi-zone indoor air quality model, and described a 17.5% to 31.6% reduction of influenza virus survival in rooms with a humidifier operating (*73*). Noti et al. used a manikin to stimulate coughs containing influenza virus and assessed the viral infectivity under various levels of relative humidity in the examination room (*74*), and found that total virus during a 1-hour collection remained at about 70% infectivity at RH ≤ 23% but only about18% at RH ≥ 43% .

Ethical considerations

No major ethical considerations.

Knowledge gaps

The exact mechanism of how humidity affects the survival of the influenza virus is not clear (*72, 75*). Many studies have studied the effect under laboratory conditions, but very few have tested in natural settings.

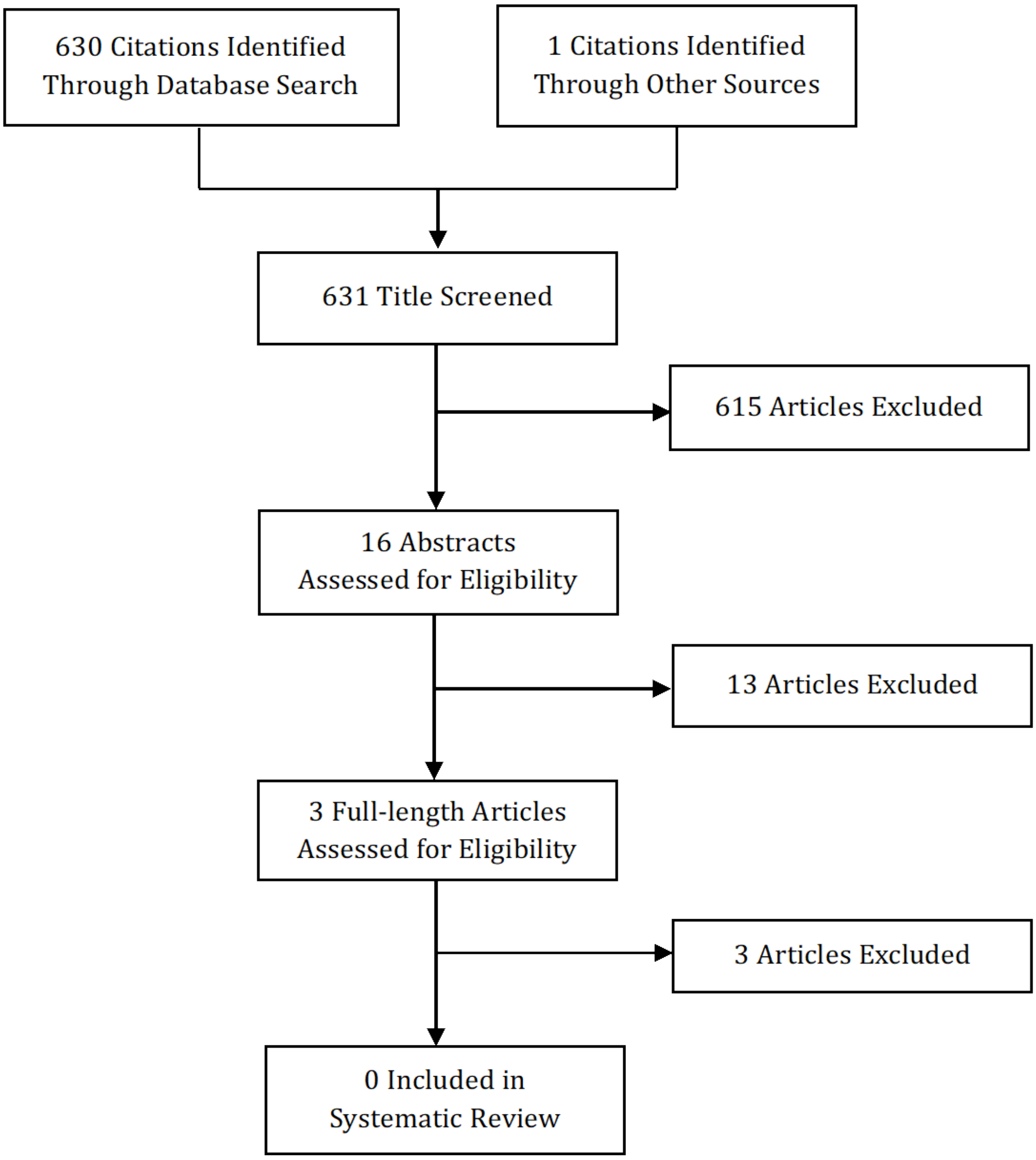


Fig. 14. The flow chart of the process and results of study selection

3. SOCIAL DISTANCING MEASURES

3.1. Contact tracing

Terminology
Contact tracing is the identification and follow-up of persons who may have come into contact with an infected person (76). 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.

Methods
A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 12 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 non-health care settings. No limitation on study design was applied for study inclusion because preliminary works have identified no RCTs for this topic. Systematic reviews and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was not conducted because no epidemiological study was included in this systematic review.

Results
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 Fig.15.

All four studies were simulation studies (*77-80*). None studied contact tracing as a single intervention; instead, this measure was studied in combination with other interventions, such as quarantine, isolation and provision of antiviral drugs (Table 14). Such combinations of interventions have been suggested to reduce transmission and delay the epidemic peak (*77, 79, 80*).

Reduction of impact
Wu et al. suggested 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 reduced the infection attack rate to 34% from the baseline of 74% (*77*). 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 individuals. On the other hand, Fraser et al. found that it would be difficult to control influenza even with 90% contact tracing and quarantine, due to the presumed high level of presymptomatic or asymptomatic transmission in influenza (*79*).

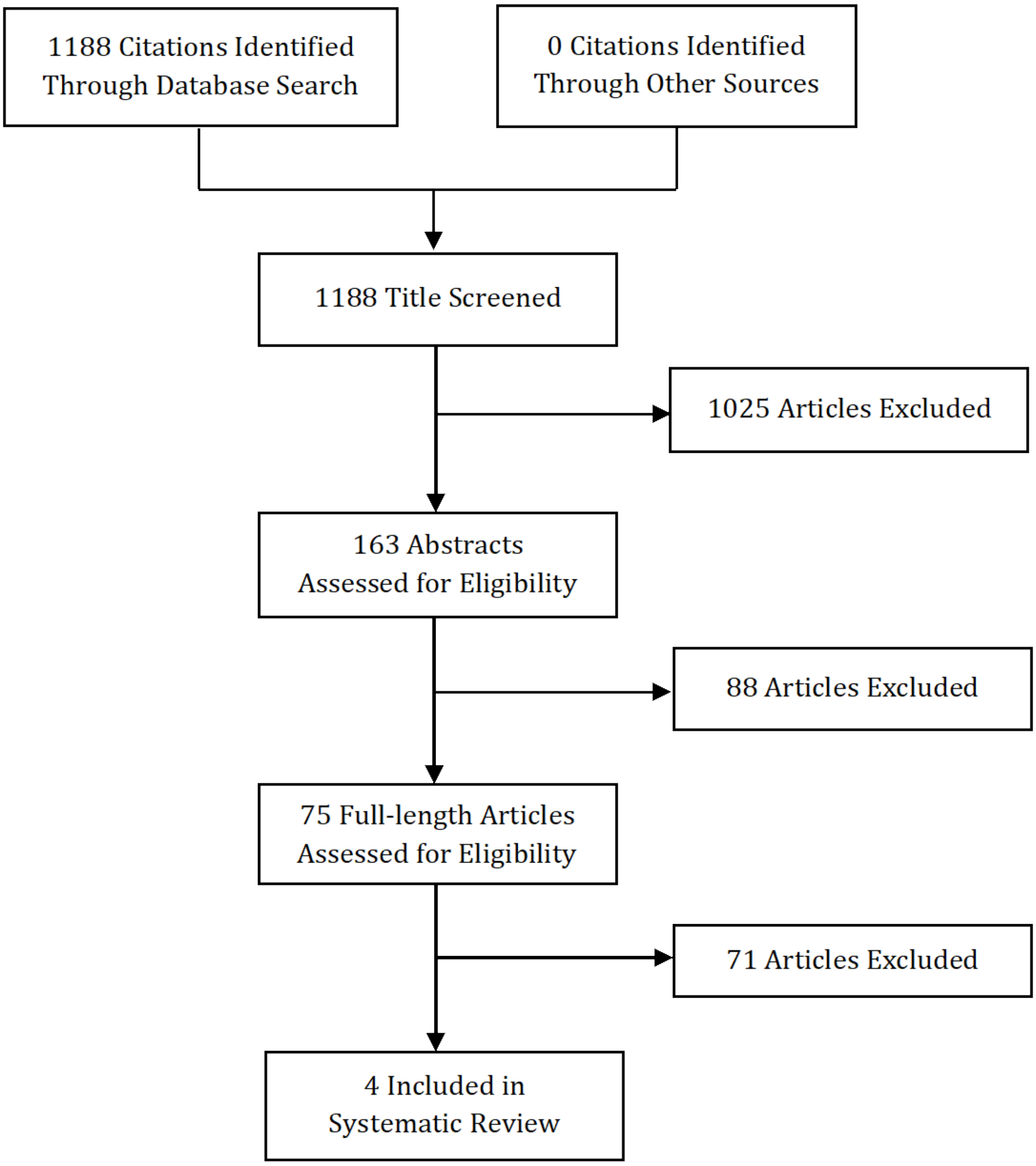


Fig. 15. The flow chart of contact tracing

Delay of epidemic peak

A combination of isolation, treatment of cases, contact tracing, quarantine and post-exposure prophylaxis for both community and household contacts, in addition to some household-focused measures, have been suggested to bring about delay in epidemic peak for up to 6 weeks, assuming a case detection rate of 10–30% (*80*). The study was set in the population structure of Germany in an epidemic with an R0 of 1.58. The authors assumed that the above combination of measures would be 75% effective in reducing secondary cases, while household-focused measures would be 50% effective.

Table 14. Summary of included studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (in schools and workplaces)	Combination of contact tracing with other interventions such as quarantine, isolation and antivirals. When contact tracing was in effect, each compliant adult member of a household named on average five members of their peer group. Contacts were traced with a mean delay of 1 day. Contacts were asked to take precautionary measures. Interventions were active before arrival of infected individuals in the city	Combination of quarantine, isolation and antivirals reduce the baseline infection attack rate of 74% to 40%. Addition of contact tracing further reduce infection attack rate to 34%, but increase proportion of population in quarantine considerably
Peak CM, 2017 (*78*)	1.54	Initial infected population of 1000 individuals in early epidemic phase, assuming no substantial depletion of susceptible within first few generations of transmission	Symptomatic contacts were isolated immediately, contacts who were asymptomatic when identified were placed under either quarantine or symptom monitoring (at high performance, delay in contact tracing was 0.5 ± 0.5 days, 90% of contacts were traced, 50% were truly infected among traced contacts)	Combination of contact tracing with quarantine is more effective in reducing reproduction number than combination of contact tracing with symptom monitoring
Fraser C, 2004 (*79*)	Upper bound of R0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household) (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%). (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate, i.e. higher R0 causes interventions to be ineffective at an earlier time point

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region.

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 R0 of 1.54 (*78*). The study suggested that contact tracing combined with quarantine was more effective than a combination with symptom monitoring in reducing transmission.

Ethical considerations

There are no major ethical issues. Identification of contacts of infected individuals does bring about privacy concerns; however, this may be justified because contact tracing does allow identification of persons at-risk and timely provision of treatment and care (81, 82). There may be more ethical concerns when contact tracing is coupled with measures such as household quarantine, discussed further in Section 3.3. As discussed in the results section above, contact tracing is able to increase substantially the proportion of people quarantined, but may not offer much additional benefit to existing interventions (*77*). A considerable amount of resources is also needed for contact tracing is these circumstances. Wu et al. suggested addition of contact tracing to existing interventions is only justified when the R0 can be reduced below 1 (*77*).

Methods

A literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search on 5 August 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 criterion is studies reporting the effectiveness of isolation on control of influenza in non-health care settings. No limitation on study design was applied for study inclusion as preliminary works have identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings were excluded. Two reviewers independently (MF and SG) screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of isolation on mitigation of influenza.

Results

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; the main reasons for exclusion of relevant articles included absence of discussion on effectiveness of isolation and focus on health care setting. One other study for inclusion was identified through snowball searches. The study selection process is detailed in Fig.16.

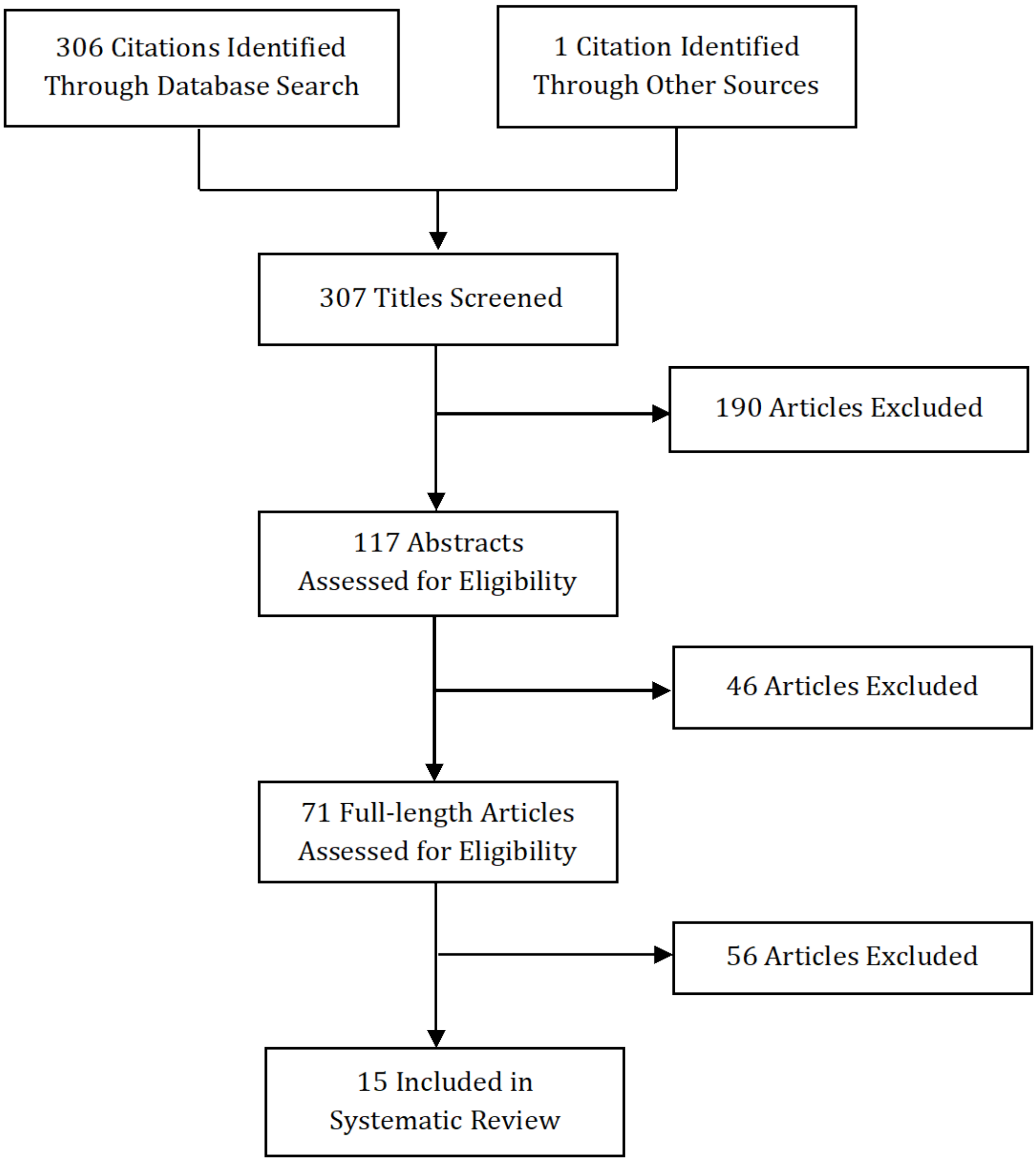


Fig. 16. The flow chart of isolation

Of the 15 included studies, four were epidemiological studies, of which one was an analysis of historical data from the 1918–1919 pandemic in 43 cities in the USA and three were outbreak investigations that occurred in a home for the elderly in France, a training camp in China and a Peruvian navy ship, respectively (Table 15) (*83-86)*. The remaining 11 were simulation studies (Table 16) (*77, 79, 87-94*). Case isolation was implemented in the outbreaks as a combination with various other interventions, such as antiviral prophylaxis and use of face mask. Case 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 a favourable impact of isolation, or combination of isolation with other interventions in epidemics with R0 1.5–2.0.

Reduction of impact

Eight studies suggested a decrease in attack rate brought about by implementation of case isolation (*77, 83, 86-91*). An individual-based simulation model for the United Kingdom and the USA suggested rapid case 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 (*87*). Kelso and colleagues reported similar findings, in which case isolation alone was able to prevent an epidemic (<10% infected) in a community of 30 000 persons with R_0 1.5, when 90% of cases are isolated and such a measure is implemented within 3 weeks from the introduction of an initial case (*90*). While isolation alone has been suggested to be more impactful than other interventions, combination with other interventions further improved the effectiveness (*77, 89-91*). In addition, the increase in isolation rate is quasi-linearly correlated with the decrease in attack rate of influenza (*88*).

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 (86). A combination of isolating ILI cases, and use of masks and hand sanitizers was implemented. The clinical attack rate of 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 attack rate recorded was about one quarter of the projected attack rate of 81% in absence of previous exposure, immunity and any interventions (*83*). In the 1918–1919 pandemic, excess death rates due to pneumonia and influenza decreased in New York City and Denver after isolation and quarantine were implemented (*85*).

On the contrary, Fraser et al. discussed the difficulty in controlling influenza even with high level of case isolation combined with contact tracing and quarantine, due to high proportion of asymptomatic transmission of influenza (*79*). The probability of isolation without increased public health effort by individuals in the community have also been suggested to be high, at 50% and 90% for adult and children respectively (*90*).

Delay of epidemic peak

The study by Flauhault et al. suggested that case isolation would have the strongest impact on global spread of a pandemic involving 52 cities, as compared to air-travel restrictions and antiviral treatment, such that isolation of 40% of cases would delay the epidemic by 83 days as compared to absence of any intervention (*88*). 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 (88). The study by Wang et al. showed a 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 (*92*). Delay in response will reduce significantly the effectiveness. Combined intervention with quarantine, school closure (SC), community-contact reduction, and personal protective measures further augmented the effect (*91*).

Table 15. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Chu C, 2012 (*83*)	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, cancellation of training and group activities, face mask usage, ventilation and disinfection (implemented within a few days of surge in ILI)	(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%	Very low
Gaillat J, 2008 (*84*)	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 post-exposure prophylaxis were given to residents and staffs	No new case was reported among residents and staffs within 2 days of implementation of intervention	Very low
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all three interventions. Cities that started implementation earlier had lower peak mortality and total mortality. (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Vera DM, 2014 (*86*)	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 usage and hand hygiene, and antiviral provision	(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%.	Very low

GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; R0: basic reproductive number; SC: school closure; USA: United States of America.

Table 16. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Flahault A, 2006 (*88*)	Constant (3.1) in tropical zone, 0.3–3.24 elsewhere with seasonal differences	(1) Spread of influenza pandemic to 52 cities globally from Hong Kong SAR via air transport (2) 25% of the population has pre-existing immunity, 60% of cases are symptomatic	(1) Combination of isolation (exclusion of 10% of symptomatic individuals from simulation) and 60% air traffic reduction (implemented since day 1) (2) Combination of (1) with antiviral treatment and vaccination	(1) Isolation reduced case number by 9% (2) Combination of isolation and air traffic reduction delayed time to reach epidemic status (1/100 000) in each city by an average of 19 days (3) Increasing isolation proportion to 40% delayed epidemic by an average of 83 days; combination of isolation, air traffic reduction, antiviral, vaccination reduced case number by 65%
Fraser C, 2004 (*79*)	Upper bound of R_0 was 21	(1) Disease outbreak in its early stages in a community of homogenous mixing (2) Proportion of presymptomatic transmission is 30–50%	Isolation of symptomatic individuals, contact tracing and quarantine of a proportion of contacts that are infected prior to isolation of symptomatic individual. Isolation and quarantine were implemented without delay. Efficacy of isolation of symptomatic individuals considered were 75%, 90%, and 100%; contact tracing and isolation of infected contacts were 100% effective.	Control of influenza is very difficult even at 90% quarantine and contact tracing, due to the high level of presymptomatic transmission.
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people) (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of home isolation of ascertained cases (compliance 60% or 90%; isolated in but not from household members) with quarantine and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 of 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–46.8%
Kelso JK, 2009 (*90*)	1.5, 2.5, and 3.5	(1) Population of 30 000, grouped into hubs of schools, workplaces and other facilities. Other contacts were biased towards meetings between neighbouring individuals (2) Asymptomatic fraction matched seasonal influenza	(1) Isolation (assumed isolated individuals only made household contacts, 90% and 100% chance respectively for adults and children to be compliant) (2) Combination of isolation with SC, workplace non-attendance and community-contact reduction	(1) At R_0 of 1.5, case isolation implemented within 3 weeks was the only single intervention capable of preventing an epidemic (≥10% attack rate), daily attack rate reduced from 90/10,000 to < 35 if introduced within a month (2) Combination of all four measures reduced attack rate from baseline of 33% to 9%, influenza control is more difficult at higher R_0

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Saunders-Hastings P, 2017 *(91)*	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of isolation with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and quarantine; best guess for adherence for voluntary isolation is 30%	(1) Combination of isolation and quarantine resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of isolation, quarantine, SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Zhang Q, 2015 *(94)*	2.5	(1) A community of households with distribution of household sizes based on Australian census data in 2001 (2) Chances of infection from community contacts is negligible as compared to infection from household member	Self-isolation or combination with antiviral prophylaxis (self-isolation assumed to have no impact on household contacts)	Self-isolation is able to overcome negative effect of delay in antiviral drug provision of 1 and 2 days by reducing household reproduction number, albeit compliance for self-isolation have to be significantly higher for 2-days delay
Zhang Q, 2014 *(93)*	1.5	(1) Stable population with homogenous mixing (2) Asymptomatic fraction is 0.5, and symptomatic cases are twice as infectious	Isolation or combination with antiviral prophylaxis	(1) Case isolation reduced reproduction number to below one (2) Combination of isolation and antiviral prophylaxis reduced substantially the cumulative number of infected individuals
Ferguson NM, 2006 *(87)*	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Rapid case isolation (assumed uniform reduction of contact including household contacts)	Rapid case isolation reduced cumulative attack rates from 34% to 27% for R0 2.0 if 90% of cases were isolated
Wu JT, 2006 *(77)*	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days (3) 70% of transmission occur outside home (e.g. in schools and workplaces)	Combination of isolation and voluntary quarantine. Interventions were active before arrival of infected individuals in the city.	Combination of isolation and voluntary quarantine reduced the baseline attack rate of 74% to 43%.

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wang L, 2012 (*92*)	1.75	International spread of influenza to cities at early stage of a pandemic outbreak	Isolation (implemented by removing some infectious individuals from the simulation model)	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 (*95*)	A(H1N1)pdm09	Community of 8800 individuals, with family structures based on Japanese census data	Home isolation of one in three adults and 70–90% of school-aged children	Total number of infections reduced by 33% when one in three adults and all children were isolated at home compared to baseline situation

R_0: basic reproductive number; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Reduction in transmissibility
Zhang et al. showed in their simulation studies that isolation of cases can reduce the household reproduction number to below one, and compensate for a delay in antiviral drug distribution by 1 to 2 days. Compliance for self-isolation has to be significantly higher to offset longer delays (*93, 94*). An outbreak in a home for the elderly in France reported an abrupt cessation of outbreak after case isolation, antiviral treatment and prophylaxis were implemented (*84*). Reduction in eproduction number was also recorded in the navy ship outbreak previously described, by 54% from 1.55 to 0.7 with a combination of interventions (*86*). The projected reproduction number without implementation of isolation was 4.5.

Ethical considerations
Home isolation is commonly done voluntarily by ill individuals who do not feel well enough to work or engage in other daily activities (*88, 90*). Some ethical concerns may arise when isolation interventions are mandated, of which the main concern is freedom of movement (*96*). Studies on acceptability of isolation as an intervention to control influenza have also suggested the potential of social stigma as a concern for some individuals (97). Home isolation may also bring about increased risks of infection among household members, in the circumstances in which the contact rate between the infected individual with household members increase due to home isolation. Such risks can be reduced by adopting good precautionary measures such as wearing a face mask or employing hand hygiene. Such concern is more significant when concurrent quarantine of household members is mandated.

Knowledge gaps
Most currently available studies on effectiveness of isolation are simulation studies, which have a low strength of evidence. Available epidemiological studies studied isolation together with other interventions, or did not use laboratory confirmation as the outcome of interest. Although it is difficult to study isolation in an RCT, robust findings from such studies would be very valuable. In addition, in some of the relevant simulation studies, assumptions have been used to predict the effect of isolation on social contact rate, which in turn affect the transmission dynamics and control of influenza. Limited information exists at present for this aspect, as well as other commonly used assumptions including asymptomatic fraction, and dynamicity due to the nature of compliance behaviour, resource planning and distribution capacity (*77*).

3.2. Quarantine of exposed individuals

Terminology
Terms relevant to quarantine are defined in Table 17.

Table 17. 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 (*98*).
Household quarantine	Confinement (commonly at home) of non-ill household contacts of a person with proven or suspected influenza (*2, 98*).
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.

TERM	DEFINITION
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 (*98*). 2) Measures taken by health care workers who chose to stay away from their families when off-duty so as not to carry the infection home (*98*).
Maritime quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a ship is permitted in a jurisdiction (*99*).
Onboard quarantine	Monitoring of all passengers and crew for a defined period before disembarking from a flight is permitted (100). Also known as 'airport quarantine' (*100*).

Methods

Literature search was conducted using PubMed, MEDLINE, EMBASE and CENTRAL (search date 24 July 2018). No language limit was applied for the literature search; however, literatures in languages other than English were excluded during full-text screening. Studies reporting the effectiveness of quarantine on the control of influenza in non-health care settings were included. No limitation on study design was applied for study inclusion as preliminary works identified no RCT for this topic. Systematic review and meta-analyses, as well as studies involving clinical settings, were excluded. Two reviewers (MF and SG) independently screened the titles, abstracts and full texts to identify articles for inclusion. Quality assessment of evidence was conducted for epidemiological studies for effectiveness of quarantine on mitigation of influenza.

Results

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 health care setting. The study selection process is detailed in Fig.17.

The included studies were comprised of 10 simulation studies (Table 19) (*77, 80, 87, 89, 91, 101-105*). The epidemiological studies included one modelling study based on pandemic influenza A(H1N1)pdm09 transmission in Beijing (106), two analyses of historical data (1918–19 influenza pandemic in the USA and South Pacific, respectively) (*85, 99*), two observational studies and one a quasi-cluster-RCT in Japan (Table 18) (*100, 107, 108*). Quarantine measures studied include home quarantine, household quarantine, border quarantine as well as maritime quarantine. Quarantine were studied as a single intervention or as 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.

Reduction of impact

Five studies suggested reduction in attack rate with implementation of household quarantine measures (77, 87, 89, 91, 107). Miyaki and colleagues conducted a quasi-cluster RCT in Japan in 2009–2010, which involved two clusters of company workers; the intervention was voluntary waiting 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 (107).

Ferguson et al. reported in their simulation study that household quarantine were effective in reducing attack rate at R0 1–4.2, especially at low values (87). Combination of quarantine with other interventions such as household isolation with prophylaxis, SC and workplace distancing were suggested to further reduce the cumulative incidence of infections (77, 87, 89).

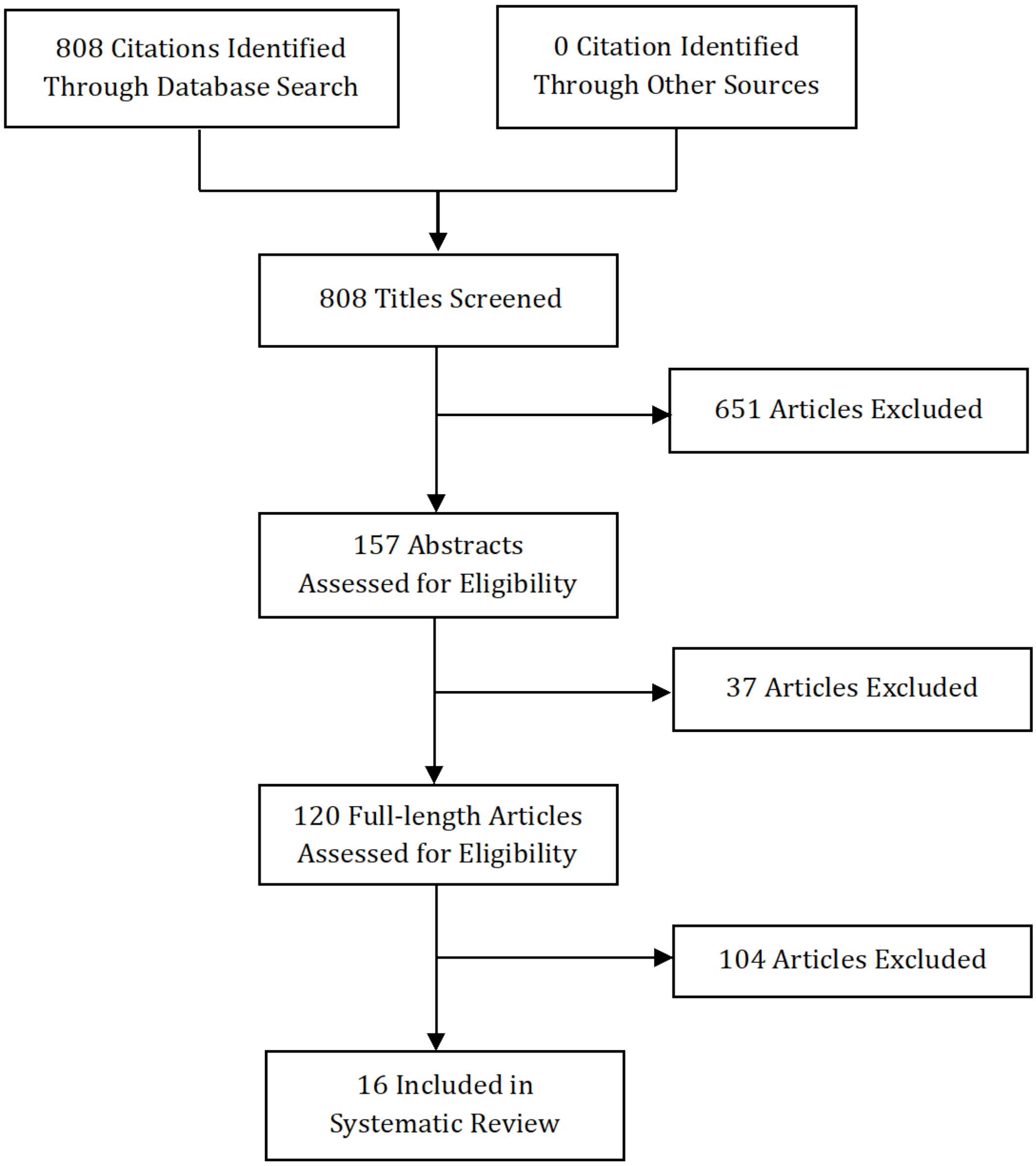


Fig. 17. The flow chart of quarantine

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 (*105*). 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 R0, in addition to early implementation (*101*). On the other hand, border quarantine has been suggested to cause minimal impact on reduction of number of cases (*104*).

Both analyses of historical data of the 1918–19 pandemic studied the effectiveness of interventions on mortality (*85, 99*). When a combination of isolation and quarantine was implemented, excess death rates due to pneumonia and influenza were shown to decrease in New York City and Denver (*85*). Maritime quarantine in the pacific islands have also delayed or prevented arrival of the epidemic, indirectly reducing mortality in the region (*99*).

Transmissibility

Both household quarantine and border quarantine have been suggested to reduce transmissibility, albeit with moderate effectiveness (*100, 102, 103*). Fujita et al. reported in their assessment of onboard quarantine inspection in Japan during the 2009 H1N1 pandemic, 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 travellers (*100*). Nishiura and colleagues also suggested that border quarantine of 9 days would prevent 99% of entry of infectious travellers into small island nations (*102*).

Increased risk to household contacts

While reducing risk and number of infections in the intervention cluster, the quasi-cluster RCT of Miyaki et al. also reported that more individuals fell ill in the intervention group when there was an ill family member (*107*). 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 (*108*).

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
Markel H, 2007 (*85*)	1918 pandemic H1N1	Analysis of historical data	43 large cities in the USA; utilized historical mortality data from the US Census Bureau and other historical archival documents	Combination of SC, public gathering bans, and isolation and quarantine (enforced and mandated respectively)	(1) All 43 cities implemented at least one intervention, and 15 cities implemented all 3 together. Cities that started implementation earlier have lower peak mortality and total mortality; (2) Excess death rate in New York decreased to baseline when isolation and quarantine were implemented, similarly in Denver when SC, isolation and quarantine were implemented	Very low
Fujita M, 2011 (*100*)	A(H1N1)pdm09	Observational	Japan (passengers at Narita International Airport for onboard quarantine and Japan at-large for the outbreak)	Onboard quarantine was conducted for 500 flights carrying 120 069 passengers in Narita International Airport over 25 days. Patients identified by positive rapid test, and persons seated around them were isolated. If patient was subsequently confirmed of their infection by PCR, patient was isolated while persons seated around them were quarantined	Onboard quarantine detected few cases and was not effective in preventing virus entry into the country, however onboard quarantine improved traceability of travellers. Upon monitoring after travellers are in town, onward transmission/ secondary infection is prevented	Very low
Li X, 2013 (*106*)	A(H1N1)pdm09	Model based on epidemiologic dynamics of influenza A(H1N1)pdm09	Beijing (N = 20 million); utilized data of daily confirmed cases reported by Beijing Municipal Bureau of Health (May-July 2009)	Mandatory quarantine for all close contacts	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	Very Low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 18. Summary of epidemiological studies

AUTHOR, YEAR PUBLISHED	INFLUENZA STRAIN OR TRANSMISSIBILITY (R_0)	TYPE OF STUDY	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS	GRADE EVIDENCE
McLeod MA, 2008 (*99*)	1918 pandemic H1N1	Analysis of historical data	South Pacific islands (including Australia); utilized archival data from national archives of relevant countries, government departments and international organizations	Maritime quarantine (monitoring all passengers and crew for on average 5–7 days before allowing disembarkation)	Strict maritime quarantine have delayed or prevented arrival of the pandemic in said jurisdictions, and associated with reduced mortality rate. Partial quarantine (routine release, without quarantine of asymptomatic passengers) in Fiji and Tahiti was unsuccessful, as in other jurisdictions that did not adopt any border control interventions	Very low
Miyaki K, 2011 (*107*)	A(H1N1)pdm09	Quasi-cluster-RCT	15 134 general employees (aged 19–72 years) of two sibling companies in Japan	Employees in intervention group were asked to stay home voluntarily if any co-habiting family members showed signs of ILI, until 5 days had passed since the resolution of ILI symptoms or 2 days after alleviation of fever, while on full pay. Employees in the control group reported to work as usual even if a household member developed ILI	Infection in workplace is significantly reduced among intervention group, however participants in this group are at higher risks of getting infected when there is an infected household member	Low
van Gemert C, 2011 (*108*)	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	Odds of a household contact who was concurrently quarantined with the index case-patient becoming a secondary case-patient increased for each additional day (adjusted odds ratio 1.25, 95% CI 1.06–1.47)	Very low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number; RCT: randomized controlled trial; SC: school closure; USA: United States of America.

Table 19. Summary of simulation studies

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
an der Heiden M, 2009 (*80*)	1.34, 1.58, 2.04	(1) Model based on the age distribution and size of the population of Germany: 71 000 000 adult population and 11 000 000 children (< 15 years old), entire population is fully susceptible at onset of the epidemic; (2) Children are 2.06 times as susceptible as adults, 86% of infected individuals become symptomatic	(1) Intensive case-based measures (CCM1; consisting of isolation and therapy of cases, contact tracing, quarantine and post-exposure prophylaxis of selected contacts in- and outside of the household); (2) Less-intensive measures (CCM2; isolation and therapy of cases, quarantine and post-exposure prophylaxis of household contacts); CCM1 and CCM2 were set to be 75% and 50% effective in reducing secondary cases	(1) When the first 500 cases are managed with CCM1 followed by 10 000 cases managed by CCM2, the peak of epidemic is delayed for up to 6 weeks (R0 1.58, 5 imported cases per day, case detection rate 10–30%). If only CCM1 was adopted without CCM2, delay was estimated to be 6–20 days (case detection rate 10–30%); (2) Effectiveness of these combination of interventions is affected by the R0 of the influenza strain and case detection rate (i.e. higher R0 causes interventions to be ineffective at an earlier time point).
Saunders-Hastings P, 2017 (*91*)	1.5–2.5	(1) Model based on population of Ottawa–Gatineau census metropolitan area in 2011	Combination of quarantine with other interventions including vaccination, antiviral treatment, prophylaxis, SC, community-contact reduction, personal protective measures and isolation; best guess for adherence for quarantine is 15%	(1) Combination of quarantine and isolation resulted in reduction of attack rate to 33.9%, from the baseline of 53.4%, lowest among all interventions studied. (2) Combination of quarantine, isolation SC, community-contact reduction and personal protective measures reduced attack rate to 15.2% and delayed pandemic peak to more than 100 days
Ferguson NM, 2006(*87*)	1.4–2.0	(1) Model based on population density data and data on travel patterns of the USA and United Kingdom; (2) 30% of transmission occurred in household, the rest in general community, workplaces and schools; asymptomatic fraction was 0.5	Voluntary household quarantine for 14 days (assumed 50% compliance, external contact rates reduced by 75% and intra-household contact rate increased by 100%)	Voluntary household quarantine was effective in reducing attack rates in the community and delaying epidemic peak, in the circumstance where compliance is high. A combination of household quarantine and antiviral prophylaxis provision will further strengthen the effect, at the same time alleviate the ethical dilemma of household quarantine

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Wu JT, 2006 (*77*)	1.80	(1) Model based on distribution of household sizes and average numbers of children in household of different sizes in Hong Kong SAR; (2) Constant introduction of 1.5 infected individuals per day per 100 000 people for 365 days; (3) 70% of transmission occur outside home (in schools and workplaces)	Combination isolation and voluntary quarantine (household quarantine of on average 7.5–8.2 days). Interventions were active before arrival of infected individuals in the city	Combination of isolation and voluntary quarantine reduced the baseline infection attack rate of 74% to 43%
Halloran ME, 2008 (89)	1.9–2.1, 2.4 and 3.0	(1) Model based on population of Chicago (8.6 million people); (2) 67% of influenza infections are symptomatic, case ascertainment levels are 60–80%	Combination of household quarantine (for 10 days with compliance of 30%, 60% or 90%) with isolation, and other social distancing measures, implemented at intervention threshold of 1, 0.1, and 0.01%	At R_0 1.9–2.1, 60% ascertainment and 90% compliance, intervention threshold of 0.1%, attack rate was 0.17–1.2%, as compared to baseline scenario of 42.4–44.7%
Sato H, 2010 (104)	2.3	(1) Population of 100 000 individuals (2) Transmission caused by cases undetected by onboard quarantine	Onboard quarantine combined with SC and home quarantine (with compliance of 10%, 30% and 50%; quarantined individuals were assumed to have no contact with infectious individuals for 3, 7 or 14 days)	The interventions were effective in reducing maximum number of daily asymptomatic cases and delaying the epidemic peak. Such effectiveness depends heavily on compliance; low compliance result in minimal impact. Home quarantine for 14 days with compliance of 50%, starting on day 6 was the most effective, which reduced number of cases by 44% and delayed the epidemic peak by 17 days
Longini IM Jr, 2005 (101)	1.4	Population of 500 000 individuals, with age and household sizes based on the Thai 2000 census (rural Thailand)	Household quarantine (contact probabilities within households and household clusters were doubled for quarantined individuals)	Household quarantine alone was effective in reducing number of cases. Early implementation and high compliance are needed for successful intervention

AUTHOR, YEAR PUBLISHED	TRANSMISSIBILITY OF THE INFLUENZA STRAIN (R_0)	STUDY SETTING & POPULATION SETTING	INTERVENTION	RESULTS & FINDINGS
Nishiura H, 2009 (*102*)	1.67	Disease-free small island nation, which permitted arrival of 20 aircraft with a total of 8000 incoming individuals before closing all airports	Border quarantine – all incoming individuals were placed into routine quarantine on arrival, and were monitored for onset of symptoms. All infected individuals who develop influenza symptoms were successfully detected. Quarantine security was assumed to be fully effective and that no secondary transmission would occur in the quarantine facility	Reduction of 99% of risks of introducing infectious individuals into small island nations with quarantine period of 9 days. Combination with rapid diagnostic testing can reduce the quarantine period to 6 days
Roberts MG, 2007 (*103*)	2.0	(1) Population of one million persons (2) Proportion of symptomatic infective 67%, asymptomatic individuals have 50% infectivity as compared to symptomatic individuals	(1) Home quarantine (70% compliance) for 6 days, hence 56% of all transmission from those infected within their household is prevented. (2) Home quarantine (50% compliance), hence 40% of transmission from household contacts is prevented (3) Combination of home quarantine with SC, and targeted antiviral prophylaxis	Home quarantine alone was successful in reducing the reproduction number, as well as proportion of population infected. At higher transmissibility, R0 3.0, only the combination of home quarantine with SC and targeted antiviral prophylaxis is effective in preventing an epidemic
Yang Y, 2011 (*105*)	1.79	(1) Population of 8382 persons, with population and social structure based on the city of Eemnes	(1) Household quarantine (stay at home at all times with compliance 25%, 50%, 75%, and 100%). (2) Combination of household quarantine with SC and refrain from social activities; Delay between interventions and out-break threshold was less than one day	At 50% compliance, household quarantine reduced 22.4% and 20.8% 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 epidemic peak

CCM: combination of case-based methods; R0: basic reproductive number; SAR: Special Administrative Region; SC: school closure; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

Delay of epidemic peak
Five studies reported the effectiveness of household quarantine, border quarantine and maritime quarantine in delaying peak of epidemic (*80, 91, 99, 104, 106*). As previously described, analysis of historical data suggested maritime quarantine effectively delayed or prevented arrival of the 1918–1919 pandemic in the pacific islands. Similarly, a model based on the 2009 H1N1 pandemic in Beijing reported delay in epidemic peak as compared to a projected scenario without mandatory quarantine (*106*). Combination with other interventions may improve effectiveness of quarantine (80). Saunders-Hastings et al. reported in their simulation study that a combination of quarantine with seven other interventions including voluntary isolation, SC, and personal protective measures can delay peak of pandemic for more than 100 days (*91*). On the other hand, as for reduction of impact, Sato et al. suggested minimal impact of border quarantine in delaying epidemic peak, mainly due to the low detection rate of cases (*104*).

Ethical considerations
As with isolation, the main concern of quarantine is freedom of movement of individuals (*106*). However, such concern is more significant for quarantine, because currently available evidence on effectiveness of quarantine varies and it involves restriction of movement of some healthy or non-ill individuals. Mandatory quarantine considerably increases such ethical concern as compared to voluntary quarantine (*96*). In addition, household quarantine can increase the risks of household members becoming infected, and such risk increases with the duration of quarantine (*87, 107, 108*). A combined policy of household quarantine with household prophylaxis has been suggested to be able to alleviate such concerns (*87*). Maritime quarantine and border quarantine are subject to similar concerns. On the other hand, onboard quarantine involves a shorter duration of restriction of movement, but currently available evidence has suggested the intervention to have low cost–effectiveness and minimal impact on influenza control.

Knowledge gaps
Most of the currently available evidence on effectiveness of quarantine on influenza control was drawn from simulation studies, which have very low strength of evidence. Available epidemiological studies did not rely fully on laboratory-confirmed influenza as the outcome of interest. While acknowledging the difficulties of studying quarantine in an RCT, robust data from experimental studies would be valuable. In addition, as part of simulation studies, assumptions have been used in various aspects of model construction, of which many still require more robust evidence, such as the asymptomatic fraction among all infections, as well as the possibility of superspreaders and the nature of compliance behaviour (*77, 102*).

3.3. 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 Table 20 (*109*).

Table 20. The definition of SC terms

TERM	DEFINITION
School closure	School is closed to all children and staff.
Class dismissal	School campus remains open with administrative staff, but most children stay home.
Reactive Closure/ Dismissal	School is closed after a substantial incidence of ILI is reported among children and/or staff in that school.
Proactive Closure/ Dismissal	School is closed before a substantial transmission among children and staff is reported.

ILI: influenza-like illness.

Methods

The latest systematic review to review the effects of SCs on influenza outbreaks was published in 2013 by Jackson et al. (*110*). We conducted an additional search to update the systematic in PubMed, Medline, EMBASE and CENTRAL from 1 January 2011 to 4 September 2018. Inclusion criteria included study designs of RCTs, epidemiological studies and modelling studies reporting the effectiveness of SC in non-health care settings. Studies that described one or more influenza outbreaks, as well as the combination of SC and other NPIs, were also included. Modelling studies were included only if they used influenza surveillance data to evaluate the effectiveness of SC. Modelling studies based on stimulated data and/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 (SG and MF) independently screened titles, abstracts and full texts to identify the eligible articles. The quality of evidence was evaluated based on GRADE to assess the overall effectiveness of SC in mitigating influenza pandemics or epidemics, with seven specific metrics: reducing the epidemic peak, reducing overall attack rate, reducing incidence, reducing duration of the epidemic, reducing transmission, delaying the epidemic peak and reducing school absenteeism.

Results

The most recent systematic review was published in 2013, Jackson et al. identified 79 epidemiological studies on SCs and summarized the evidence as demonstrating that this intervention could reduce the transmission of pandemic and seasonal influenza among schoolchildren, but owing to the heterogeneity in the available data, the optimum strategy (e.g. the length of closure, reactive or proactive closure) remained unclear (*110*). The flow chart of study selection is shown in Fig. 19.

In the additional search to update the systematic review that was published by Jackson et al. in 2013, 287 papers were identified from the four databases and 12 citations were found from other sources, resulting in total of 299 citations for screening. Of these, 101 full-length articles were assessed for eligibility and 22 additional articles were identified. In total, 101 articles were included in our systematic review. The flow chart of study selection is shown in Fig. 18. The quality of evidence was assessed to be very low according to the GRADE criteria.

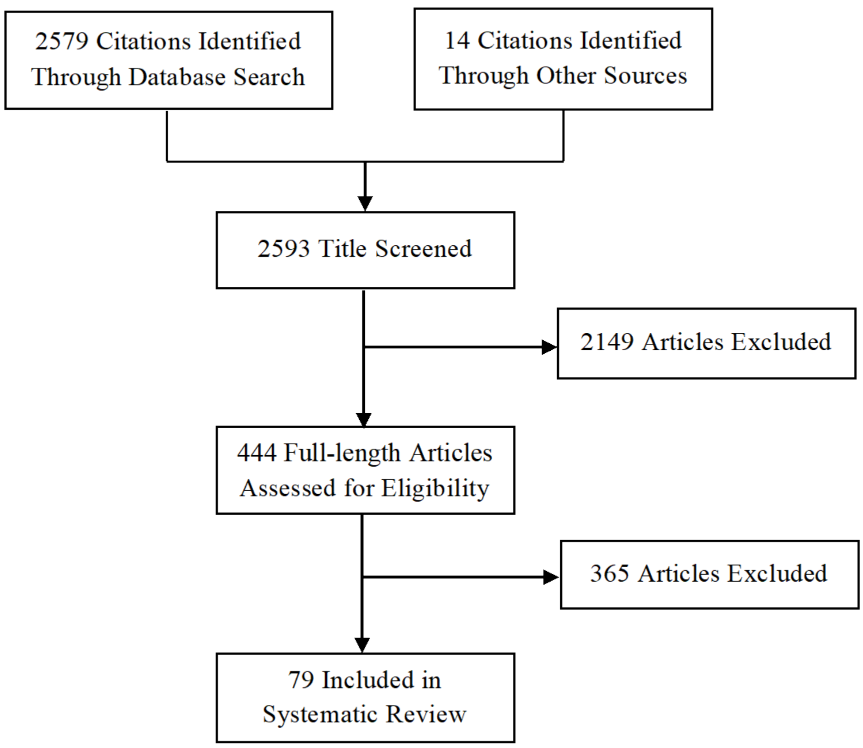


Fig. 18. The flow chart of systematic review by Jackson

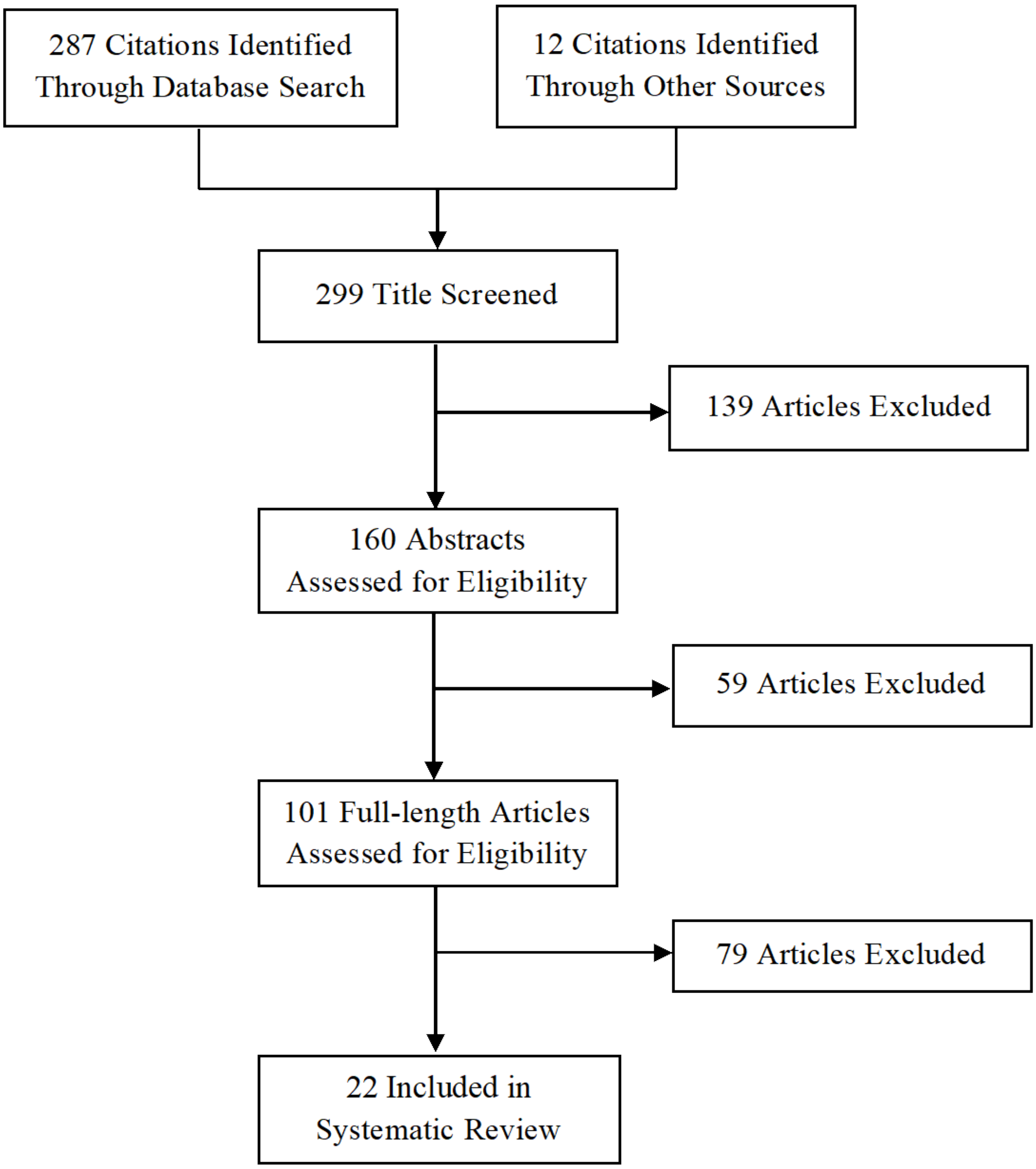


Fig. 19. The flow chart of updated studies in school closures

Among the included 101 articles, 16 articles presented data on reactive SCs (111-126), 13 articles examining proactive SCs (*85, 127-138*), 28 articles examined the impact of regular school holidays on transmission (*123, 125, 136, 139-163*), and 47 articles were related to outbreak reports or teachers' strike (*164-210*). The basic characteristic of the studies is shown in Table 21.

Table 21. Basic characteristic of the studies

	Number of 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[a]	
Outbreak report or teachers' strike	47
Planned holiday	28
Reactive closure	16
Proactive closure	13
Duration of closure[b]	
7–13 days	40
14–20 days	24
≥ 21 days	22
< 7 days	13
Varied	8
Not clear	5

[a] A single article can contain different types of closure.

[b] Each study may present more than one dataset for which the durations of closure differed.

A total of 16 studies demonstrated that reactive SC could be a useful control measure during influenza epidemics or pandemics, with impacts that included reducing the incidence and reducing the peak size (Table 22). Several studies reported a reduction in number of confirmed or ILI cases (*114, 115, 117, 119, 123, 125, 126*). One study also showed a reduction in total infected cases by 32.7% (total reduced number of cases from 127.1 to 85.5) (*122*). Another observational study suggested a reduction in the peak of influenza epidemic curve by 24% during the 4-day closure, and also a reduction of the total number of infected students by 8% (*118*). However, two observational studies in China did not identify a significant difference on total attack rate between the control (SC not implemented) and intervention group (school closed) (*112, 113*). Two studies in the USA showed that absenteeism was lower after school reopening compared to before SC (*120, 121*).

Effectiveness of SCs can also be assessed by evaluating the transmission rate; that is, reproduction number. Hens el at. showed 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 SC (116). An observational study from Japan reported that SC was more effective than class closure (dismissal of that particular class with substantial increase in influenza incidence) (126). In another study from Japan, a 2-day SC in the outbreak situation (after a 10% of absentee occurrence in a school) was also shown to associate with the interruption of an outbreak within a week (124). 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 (*111*).

Effectiveness of proactive SC was studied in 13 articles (Table 23). A study showed that proactive SC had an advantage in delaying the epidemic peak for more than a week, affecting the modelled mean peak, and reducing the overall attack rate from 9.7% to 8.6% (*127*). Bootsma et al. estimated that early and sustained interventions, including SCs, reduced overall mortality by up to 25% in some cities (128). Hatchett et al. and Markel et al. also examined NPIs in the 1918–1919 pandemic, reporting that the combined use of NPIs including SCs were able to delay the time to peak mortality, and to reduce peak mortality and overall mortality (*85, 135*).

One study estimated a 29–37% reduction in influenza transmission by the 18-day period of mandatory SCs and other social distancing measures including closure of restaurants and theatres, and cancellation events (130). A study in Mexico City estimated that effective reproduction ratio declined from 1.6 before closure to less than 1 during closure (134). Wu et al. estimated that the reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday (*138*). One study in Mexico showed a 80% reduction of contact rate during closure period and a subsequent planned holiday (*136*). However, closing kindergartens and primary schools for 2 weeks in Hong Kong SAR did not show any significant effect on community transmission, although the incidence remained low after the peak during proactive closure (133).

A total of 28 studies monitored the change of influenza incidence across planned school holidays (e.g. the scheduled winter holiday each year), to estimate the impact of SC on influenza transmission (Table 24). Eight of these studies illustrated that planned holidays could reduce influenza transmission (*136*, *139*, *141*, *147*, *148*, *150*, *159*, *163*). One study demonstrated that school holidays reduced the R0 of influenza A(H1N1)pdm09 by 14–27% in different regions of India compared with non-holiday period (139). One study also reported an association of school holiday with a reduction of 63% to 100% in transmission in Canada (148). Another study reported a reduction of R0 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 (*163*). Two studies in the United Kingdom and Mexico showed that SCs could reduce contact rate by around 48–80% (*136, 141*). Two studies in Belgium and the Netherlands suggested that holidays delayed the epidemic peak by more than 1 week, and reduced the peak incidence by 4–27% (*155, 160*). A study from the USA showed that absenteeism in Adrian reduced by approximately 6% (*157*), whereas Rodriguez et al. reported no difference between closed schools and those that did not close (*158*).

Observational studies also reported a reduction in incidence of influenza associated with planned school holidays (*123*, *125*, *140*, *142-146*, *149*, *150*, *152-154*, *156*, *159*, *161*, *162*). 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 schoolchildren to adults during the breaks (*143*, *145*, *153*). A study based on national surveillance data in France showed that routine school holidays prevented 18% of seasonal influenza cases (18–21% in children) (*142*). Another study in Japan estimated a 38% reduction in number of medically attended clinical ILI cases (*152*). Wheeler et al. suggested that planned holidays could prevent or delay potential influenza cases among school-age children by around 42% (*161*). In comparison, a systematic of simulation studies that reviewed the effects of SCs on influenza outbreaks found that this intervention can be a useful control measure during an influenza pandemic (*211*).

A study conducted a review on social distancing interventions in schools other than SC (212). A total of 16 articles met the inclusion criteria, and 16 states in the USA mentioned school practices to promote social distancing in the published guideline documents. The most frequent categories of school measures included cancelling or postponing after-school activities, increasing space among students, cancelling classes or activities, and reducing mixing during transport.

A simulation study showed that classroom restrictions (the children must remain seated while in their classroom) were the best single intervention at lower infection probabilities. At higher transmission rates, staggered shifts (each classroom follows one of three different schedules put forth by the school: the current schedule, a shift of 45 minutes, and a shift of 90 minutes) is the best single intervention (*213*). A study by Cooley et al. reported that a 3-day weekend for schools could be effective at reducing peak attack rate, and would be less detrimental than sustained SC (*214*). Closing the playground and other common areas could significantly reduce the total number of infected students (*215*). However, the evidence is limited on the effectiveness of school measures.

Ethical considerations

Apart from a potential health impact, SCs can have a substantial social impact by requiring parents to make other arrangements for care or supervision of their children, which can be particularly challenging for some families and for prolonged closures. In addition there may be social equity concerns; for example, because of access to subsidized or free food at school for lower income families (*121*).

Knowledge gaps

More research is needed on the best trigger factors, timing and duration of SCs in order to maximize the impact of this disruptive intervention.

Table 22. Summary table of reactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Cauchemez S, 2011 (*111*)	–	–	–	–	Reproduction number remained unchanged during SC and after the reopening of school (R = 0.3)	–
Chen T, 2017 (*112*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Chen T, 2018 (*113*)	–	Total attack rate of 1–3 week of SC were close to that for no intervention	–	Duration of outbreak was prolonged	–	–
Davis BM, 2015 (114) [a]	–	–	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 (115)	–	–	7.1% reduction in ILI case over the outbreak period	–	–	–
Hens N, 2012 (116)	–	–	–	– –	Influenza case reproduction number decreased from 1.33 (during outbreak before SC) to 0.43 (after SC)	–
Janjua NZ, 2010 (117)	–	–	Daily number of ILI cases declined during SC	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE DURATION	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Kawano S, 2015 (*118*)[b]	Number of infected students in a SC decreased by 24% at its peak	Cumulative number of infected students decreased by 8.0%	–	–	–	–
Loustalot F, 2011 (*119*)	–	–	Incidence remained low during closure	–	–	–
Miller JC, 2010 (*120*)	–	–	–	–	–	Absenteeism was lower after reopening compared to before closure
Russell ES, 2016 (*121*)	–	–	–	–	Closing schools after a widespread ILI activity did not reduce ILI transmission	Absenteeism changed from 1% (baseline), to 3.62% (during SC), and 0.68% (after school reopening)
Sato T, 2013 (*122*)	–	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 (*123*)	–	–	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 (*124*)	–	–	–	Outbreak duration decreased by 4.98 days if the class is closed for 2 days upon the observed 10% ILI-related absentee rate	–	–
Uchida M, 2011 (*125*)	–	–	Incidence declined during closure period	–	–	–
Uchida M, 2012 (*126*)[c]	–	–	At elementary school, subsequent peak of H1N1 case showed up despite school or class closure (Fig. 1); at junior high school, SC significant reduced the number of H1N1 case but not in class closure (Fig. 2)	–	–	–

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.

[a] ILI rate ratio is compared at school district level, with 51–100% of schools being closed, compared with district level, with 1–50% of schools being closed.

[b] Author mentioned the recommended period of SC is > 4 days.

[c] Closure duration is significantly related with the number of cases within the 7-day of school opening.

Table 23. Summary table of proactive closure

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Bolton, 2012 (*127*)	–	Overall attack rate decreased from 9.7% to 8.6%[a]	Epidemic peak would be delayed by over a week	–	–
Bootsma MC, 2007 (*128*)[b]	Earlier intervention may reduce peak mortality	Earlier intervention may reduce total mortality	–	–	–
Caley P, 2008 (*129*)[b]	–	–	–	–	Transmission reduced by 38% during period of social distancing
Chowell G, 2011 (*130*)[b]	–	–	–	–	Reproduction number decreased from 2.2 (before SC) to 1.0 (during SC); transmission rate is estimated to reduce by 29.6% during the intervention period
Copeland DL, 2013 (*131*)	–	–	–	Incidence rate of ARI increased from 0.6% (before closure), to 1.2% (during SC) and dropped to 0.4% (after school reopening)	–
Cowling BJ, 2008 (*133*)[c]	–	–	–	–	Not found a substantial effect on community transmission
Cowling BJ, 2010 (*216*)[c]	–	–	–	–	The estimated reproduction number changed from 1.5 (initial peak) to below 1 (during proactive closure), and fluctuated between 0.8 and 1.3 through the school vacations
Cruz-Pacheco G, 2009 (*134*)[b]	–	–	–	Incidence increased to peak then decreased gradually during closure period	Effective reproductive ratio R(t) declined from 1.6 before to < 1 during closure

ARI: acute respiratory infection (presence of at least 2 of the following symptoms: fever, cough, sore throat and runny nose);

ILI: influenza-like illness (fever plus cough and/or sore throat); SC: school closure.

[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.

[b] SC combined with other interventions.

[c] Proactive closure followed by planned holidays.

AUTHOR, YEAR	REDUCE PEAK	REDUCE OVERALL ATTACK RATE	DELAY TIME TO PEAK	REDUCE INCIDENCE	REDUCE TRANSMISSION
Hatchett RJ, 2007 (135)[b]	Earlier intervention reduced peak weekly excess pneumonia and influenza death rate	–	–	–	–
Herrera-Valdez MA, 2011 (*136*) [b]	–	–	–	–	Reduced contact rates by around 80% during closure period
Markel H, 2007 (85) [b]	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 (*137*)	–	–	–	Number of ILI cases decreased throughout closure period	–
Wu JT, 2010 (*138*) [c]					The reproduction number was reduced from 1.7 to 1.5 during the proactive closures and to 1.1 during the rest of the summer holiday

[a] Assuming schools were closed for 4 weeks and the attack rate in children was threefold higher than in adults.

[b] SC combined with other interventions.

[c] Proactive closure followed by planned holidays.

Table 24. Summary table of planned holidays

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Ali ST, 2013 (*139*)	–	–	–	–	Reproduction number reduced by 14–27% in different regions of India	–
Baguelin M, 2010 (*140*)	–	–	–	Incidence declined throughout the closure period	–	–
Birrell PJ, 2011 (*141*)	–	–	–	–	Reduce contact rate among 5–14 years old by 72% (summer holiday) and 48% (half term holiday)	–
Cauchemez S, 2008 (*142*)	–	–	–	Routine school holidays prevented 18% of seasonal influenza cases (18–21% in children)	–	–
Chowell G, 2011 (*144*)	–	–	–	Number of confirmed cases declined throughout closure period	–	–
Chowell,G, 2014 (*143*)[a]	–	–	–	Schoolchildren-to-adult ratios decreased by 40–68% during the 2-week period immediately preceding the winter break	–	–
Chu Y, 2017 (*145*)	–	–	–	ILI incidence rate ratio of age 5–14 (schoolchildren) to adult (aged above 60) declined by 13.3% during summer break	–	–
Davies JR, 1988 (*146*)	–	–	–	Clinical influenza cases increased during closure period	–	–
Eames KT, 2012 (*147*)	–	–	–	–	The initial growth rate of the epidemic during holidays would be 35% lower than during term time (from 1.57 to 1.07)	–

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Earn DJ, 2012 (*148*)	–	–	–	–	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 (*149*)	–	–	–	Estimated number of ILI cases declined during school holiday	–	–
Ewing A, 2017 (*150*)[b]	–	Fig. 5A suggested a peak delay	–	Fig. 5B illustrated a reduction of influenza incidence	Influenza transmission decreased by approximately 15% (from 1.1 to 0.9) in most seasons and decreased to < 1 immediately following Christmas	–
Flasche S, 2011 (*151*)	–	–	–	–	No evidence found of a relationship between the effective reproduction number and the start of school holidays	–
Fujii H, 2002 (*152*)	–	–	–	Number of ILI cases declined 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 (*153*)	–	–	–	ILI incidence rate ratio reduced by 37% among children 5–14 years of age during the week after the winter school break	–	–
Herrera-Valdez MA, 2011 (*136*)[c]	–	–	–	–	Reduced contact rates by around 80% during closure period	–

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Louie JK, 2007 (*154*)	–	–	–	ILI incidence declined throughout closure; laboratory-confirmed declined slightly first, then increased	–	–
Luca G, 2018 (*155*)[d]	Peak incidence reduced by 4%	All holidays delay the peak time of 1.7 weeks	Epidemic size reduced by approximately 2%	–	–	–
Merler S, 2011 (*156*)[e]	–	–	–	Incidence declined during closure	–	–
Monto AS, 1970 (*157*)	–	–	–	–	–	Absenteeism reduced by approximately 6% in Adrin
Rodriguez CV, 2009 (*158*)	–	–	–	–	–	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 (*159*)	–	–	–	Consultation rates decreased in school-aged children	Transmission of influenza may be interrupted in that school-age group	–
Sonoguchi T, 1985 (*123*)	–	–	–	Case number remained low during closure period in middle school	–	–
Te Beest DE, 2015 (*160*)	Epidemic peak is lowered by 27%	Peak is delayed for approximately 1 week	–	–	–	–

AUTHOR, YEAR	REDUCE PEAK	DELAY PEAK	REDUCE OVERALL ATTACK RATE	REDUCE INCIDENCE	REDUCE TRANSMISSION	REDUCE ABSENTEEISM
Uchida M, 2011 (*125*)	–	–	–	Incidence declined during closure period	–	–
Wheeler CC, 2010 (*161*)	–	–	Daily number of ILI cases declined during SC	Prevent or delay around 42% of potential influenza cases among school-age children	–	–
Wu J, 2010 (*162*)	–	–	–	Cumulative incidence of confirmed cases increased during SC	–	–
Yu H, 2012 (*163*)	–	–	–	–	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%	–

CI: confidence interval; ILI: influenza-like illness; SC: school closure.

[a] Decline 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.
[b] The holiday model combined the changes associated with both the SC and travel models.
[c] All holidays included Fall holiday, Christmas holiday, Winter holiday and Easter holiday.
[d] Mainly planned holidays, some reactive closures.
[e] SC combined with other interventions.

Table 25. Summary of outbreak reports and teachers' strike

AUTHOR, YEAR	OUTCOME
Armstrong C, 1921 (*164*)	Number of cases peaked on the day following closure and declined thereafter
Baker MG, 2009 (*165*)	Start of the school holidays in New Zealand reduced influenza transmission and that the return to school slightly accelerated the epidemic
Briscoe JH, 1977 (*166*)	Number of clinical cases declined during closure
Calatayud L, 2010 (*167*)	Cases decline after the half way of SC
Carrillo-Santisteve P, 2010 (*168*)	Number of confirmed and probable cases declined during closure
Cashman P, 2007 (*169*)	A planned SC may have contributed to controlling the outbreak without quantitative information
Chieochansin T, 2009 (*170*)	Laboratory-confirmed cases declined throughout period of closure
Cohen NJ, 2011 (*171*)	Number of respiratory illness cases were lower on the first day of closure compared to previous days, increased during closure and then declined
Danis K, 2004 (*172*)	Number of ILI cases declined during closure period
Echevarria-Zuno S, 2009 (*173*)	Epidemic continued while schools were closed and peaked around 1 week after closure
Effler PV, 2010 (*174*)	Number of confirmed cases declined during closure period
Engelhard D, 2011 (*175*)	ILI rate peaked and declined during closure
Farley TA, 1992 (*176*)	Absenteeism remained low after school reopening
Glass RI, 1978 (*177*)	School absenteeism was lower after the holiday than before
Gomez J, 2009 (*178*)	Number of pneumonia cases decreased from 130 cases at peak to around 40 during closure
Grilli EA, 1989 (*179*)	During the mid-term break there were a further 15 ILI cases (daily cases not provided)
Guinard A, 2009 (*180*)	No further cases during SC period, but epidemic appear to be over before the school was closed

AUTHOR, YEAR	OUTCOME
Health Protection Agency West Midlands H1N1v Investigation Team, 2009 (*181*)	Confirmed number of cases declined during closure period
Heymann A, 2004 (*182*)[a]	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 (*183*)[a]	Decease in ratio of 14.7% for 6–12 years old associated with teachers' strike
Hsueh PR, 2010 (*184*)	Number of class suspensions or SC generally associated with the number of hospitalizations
Huai Y, 2010 (*185*)	Number of confirmed cases peak at 30 cases on the first day of closure, then declined during closure period
Janusz KB, 2011 (*186*)	Absenteeism changed from 8% (baseline), to 15% (2-days before school outbreak), and 13% (post-school outbreak)
Johnson AJ, 2008 (*187*)	Number of parentally-reported ILI cases decline because of SC
Jordan EO, 1919 (*188*)	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 (*189*)	Number of confirmed cases declined throughout closure period
Lajous M, 2010 (*190*)	Planned holiday was followed by a slight decrease in ILI case numbers
Leonida DDJ, 1970 (*191*)	Absenteeism continued decline during second SC
Lessler J, 2009 (*192*)	Both confirmed H1N1 influenza and self-reported ILI declined through closure period
Leung YH, 2011 (*193*)	Number of laboratory-confirmed cases increased during first two days of closure and then declined
Lo JY, 2003 (*204*)	Change in proportion of positive specimens were 50–100% lower in April-June than the average because of community control measures
Marchbanks TL, 2011 (*194*)	Number of ILI cases increased during first two days of closure and then declined
Miller DL, 1969 (*195*)	In children aged 5–14 years, rates of influenza declined during the Christmas holidays

[a] Articles related to teachers' strike.

AUTHOR,YEAR	OUTCOME
Nishiura H, 2009 (*196*)	Number of laboratory-confirmed cases declined throughout the closure
Olson JG, 1980 (*197*)	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 (*198*)	Case numbers peaked and declined during holiday, effective reproduction number declined before holiday and continued to decrease during the holiday
Petrovic V, 2011 (*199*)	Weekly incidence rate of ILI and the number of hospitalized cases decreased after the SC
Poggensee G, 2010 (*200*)	Practice index was associated with vacation density
Rajatonirina S, 2011 (*201*)	Only few cases continued to occur during closure period
Shaw C, 2006 (*202*)	Absenteeism was lower after closure than before closure in both reactive closure and planned holiday
Shimada T, 2009 (*203*)	Number of new confirmed cases decreased after SCs
Smith A, 2009 (*206*)	Number of ILI cases declined during closure period
Strong M, 2010 (*207*)	Number of self-reported ILI cases declined during closure period
van Gageldonk-Lafeber AB, 2011 (*208*)	Possible reduced incidence, or slowed epidemic growth
Wallensten A, 2009 (*209*)	Absenteeism almost not changed before and after closure
WHO, 2009 (*205*)	School absenteeism in the following weeks did not increase after school reopening
Winslow CEA, 1920 (*210*)	Cities with SCs had higher deaths rates; timing and duration of closure were not stated

ILI: influenza-like illness; SC: school closure.

3.4. Workplace closures

Methods

PubMed, Medline, EMBASE and CENTRAL were searched until 18 September 2018. No language limits were applied but papers in languages other than English were excluded in screening. The inclusion criteria included RCTs, epidemiological studies and simulation studies reporting the effectiveness of workplace closure (WC) in non-health care settings, as well as the combination of WC and other NPIs. The exclusion criteria included the following: studies in health care settings; studies do not have specific data related to WC; review, letter, news or summary articles; studies related to avian influenza; and the language of articles not in English. Two reviewers (SG and ES) independently screened titles, abstracts and full texts to identify eligible articles.

Results

A total of 475 citations were identified through database search and other sources, of which 18 full-length articles assessed for eligibility and six articles were selected for this systematic review. The flow chart of study selection is shown in Fig. 20.

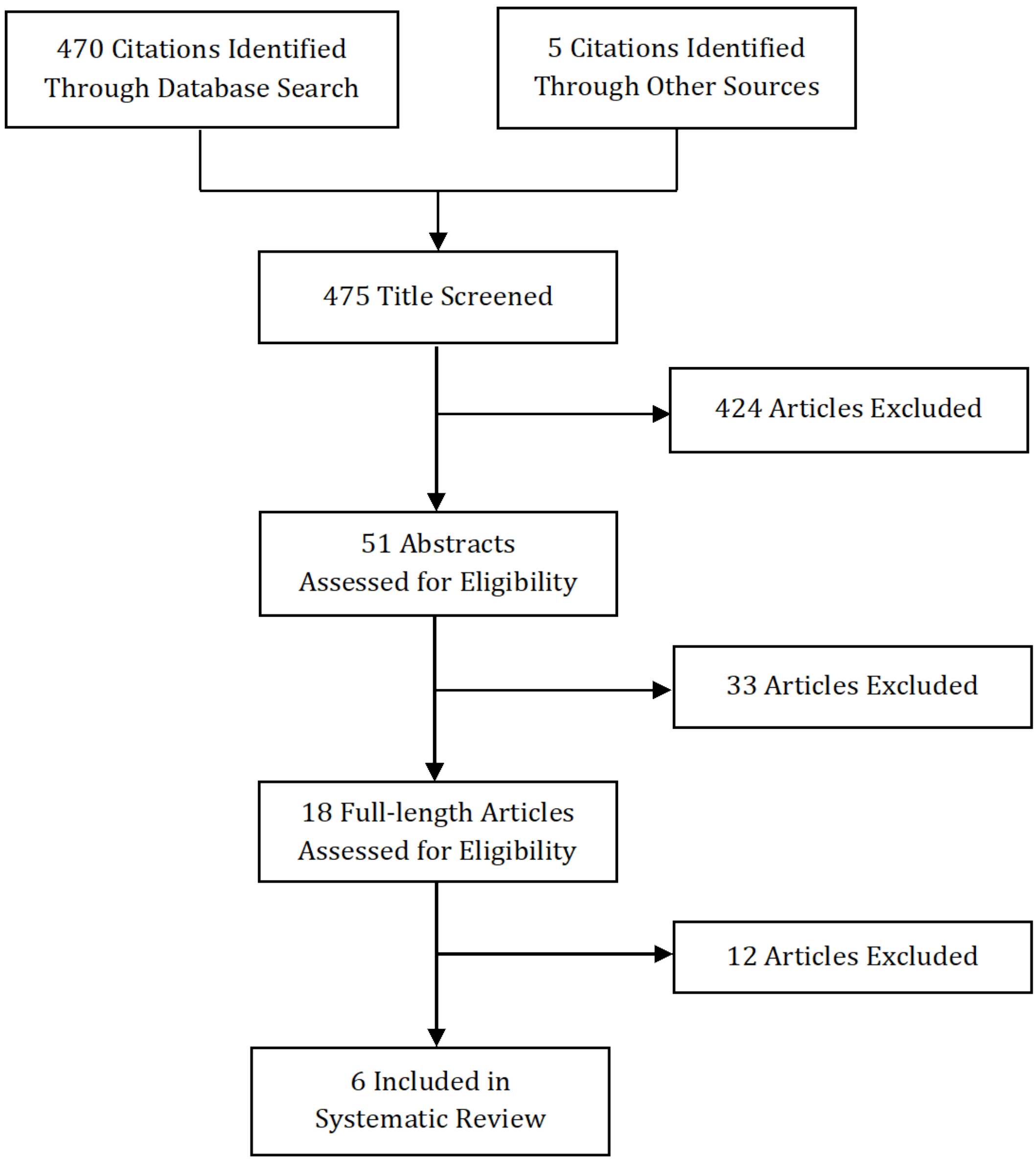


Fig. 20. The flow chart of workplace closure

Among these six studies, four were measured with SC, one targeted different single and multiple strategies, and another evaluated the effectiveness of WC alone (Table 26). All six studies represented simulation studies that met the inclusion criteria and the main outcome include the reduction of attack rate, peak number and delay of epidemic peak.

Predicted effects reduction

Five studies suggested the reduction in attack rate, infected duration or peak number. In the studies by Ferguson et al. (*87*) and Xia et al. (*217*), WC resulted in a small reduction in cumulative attack rate, while Carrat et al. (218) and Mao et al. (*219*) suggested an obvious decrease when assessing the effect of combining intervention. The study by Carrat et al. simulated individual and community level model in France, which suggested a decline of the cumulative attack rate from 46.8% to 1.1%, assuming the R0 of 2.07 (*218*). Mao et al. used an agent-based stochastic simulation model with R0 = 1.3–1.4 in the USA, and predicted a decline of overall attack rates from 18.6% to 11.9% with 100% SC and 10% WC, and from 18.6% to 4.9% with 100% SC and 33% WC (*219*).

A heuristic model using R0 of 1.7 and 2.0 suggested a small reduction in cumulative attack rate but a more substantial reduction in peak attack rates (up to 40%) when 100% SC and 10% WC was implemented. It also suggested that effectiveness could increase if 50% of workplaces were closed, but this would have a higher economic cost (*87*). A simulation model for the control of influenza in an isolated geographical region by Roberts et al. suggested the single WC strategy could not prevent the epidemic (with R0 = 2.0).

Delay the time of peak occurrence

Delaying the epidemic peak is another factor to consider the effectiveness of this intervention. 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, depending on the R0 = 1.4, 1.7 and 2.0 (*220*). However, the study by Mao et al. suggested that 100% SC and 33% WC could advance the peak by approximately 1 week (*219*).

Ethical considerations

Apart from a potential health impact, WC can have a substantial impact on the economy and productivity of the society (*221*).

Knowledge gaps

As with SCs, more research is needed on the best trigger factors, timing and duration of WCs in order to maximize the impact of this disruptive intervention.

Table 26. Description of studies included in the review of WCs

STUDY	INFLUENZA STRAIN & TRANSMISSIBILITY (R_0)	STUDY SETTING AND POPULATION	STUDY DESIGN	CLOSURE DURATION	CLOSURE PROPORTION	CLOSURE THRESHOLD	INTERVENTION	OUTCOME
Carrat F, 2006 (*218*)	Future pandemic strain; R_0 = 2.07	General population in France (n = 10 000)	Simulation both individual and community level	N/A	N/A	5 infections per 1000 subjects	SC + WC	Mean accumulation infection rate reduced from 46.8% (42.3–50.5%) to 1.1% (0.6–2.1%)
Ciofi degli Atti ML, 2008 (*220*)	Future pandemic strain; R_0 = 1.4, 1.7, 2	General population in Italy (n = 56 995 744)	Global SEIR model for importation of cases with an individual-based model	4 weeks	N/A	N/A	SC + WC	Nationwide closure could delay the time of peak occurrence by 5–8 days, based on various scenarios
Ferguson NM, 2006 (*87*)	Future pandemic strain; R_0 = 1.7, 2.0	300 million in USA, 58.1 million in United Kingdom	Heuristic model	N/A	Varied: 10%, 50%	N/A	100% SC + varied WC (10%, 50%)	100% SC + 10% WC could slightly reduce the cumulative attack rate, and might reduce the peak attack rate of up to 40%; 50% of WC could further improve the effectiveness with a higher economic cost
Mao L, 2011 (*219*)	Future pandemic strain; R_0 = 1.3–1.4	Urbanized area of Buffalo, NY, USA (n = 985 001)	Agent-based stochastic simulations	N/A	Varied: 10%, 33%	N/A	1) 100% SC + varied (10%, 33%) WC; 2) 100% SC + varied (10%, 33%) WC + preventive behaviour	1) Overall attack rates declined from 18.6% to 11.9% (10% WC) and 4.9% (33% WC), respectively 2); overall attack rate reduced to 3.99% (10% WC) and 1.83% (33% WC), respectively
Roberts MG, 2007 (*103*)	Future pandemic strain; R_0 = 1.1, 2.0 and 3.0	Isolated geographical region (n = 1 000 000)	A model based on published parameters	N/A	70%	N/A	1) WC; 2) WC + SC; 3) WC + SC + antiviral treat + 70% home quarantine	The single strategy of WC is not successful, the combination of four strategies would prevent the epidemic
Xia H, 2015 (*217*)	Simulate H1N1; R_0 = 1.35, 1.40, 1.45, 1.60 (all similar to R_0 = 1.35)	Delhi, India (over 13 million)	Realistic individual-based social contact network and agent-based modelling	3 weeks	60%	Over 0.1% population are infected	Single: WC	Intervention could reduce the attack rate and peak number, and delay the time of peak occurrence; single WC is the most ineffective method among vaccination, antiviral drugs, SC and WC

N/A: not applicable; NY: New York; R0: basic reproductive number; SC: school closure; SD: standard deviation; SEIR: susceptible–exposed–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America; WC: workplace closure.

3.5. Workplace measures

Methods

The latest systematic review to review the effects of workplace measures in reducing influenza virus transmission was published by Ahmed et al. in 2018 (*222*). We conducted an additional search in PubMed, Medline, EMBASE and CENTRAL from 1 January 2017 to 28 September 2018. Workplace measures includes teleworking, flexible leave policies, working from home, weekend extension, segregation into smaller groups and social distancing at workplaces. All RCTs, epidemiological studies or simulation studies in non-health care workplaces were included in this review. Review, commentary, editorial articles, studies on WC and studies on generic social distancing not in workplace were excluded from our review. The following outcomes were extracted from the studies: cumulative attack rate, peak attack rate, occurrence of peak and other effects. Two reviewers (SG and ZX) worked independently. The GRADE method was used to evaluate the quality of evidence for the effectiveness of workplace measures in reducing influenza transmission.

Results

The most recent systematic review was published in 2018; Ahmed et al. identified 15 epidemiological or simulation studies (from 14 articles) on workplace measures. In the additional search to update the systematic review that was published by Ahmed et al., 81 articles were identified from the databases and one paper from other sources, resulting in total of 82 for title screening. Ten full-length articles were assessed for eligibility and four additional articles were identified. In total, 19 studies (18 articles) were included in our systematic review. The flow charts of study selection are shown in Fig. 21 and Fig. 22.

Among the included 19 studies, there were six epidemiological studies (Table 27) (*107, 223-227*). A cross-sectional study that randomly selected US adults from the Knowledge Networks online research panel showed that those who could not work from home from 7 to 10 days were more likely to have ILI symptoms compared to those who could (*223*). Another cohort study suggested that respondents who could work from home had a 30% lower rate of attending work with severe ILI symptoms compared to employees without such ability, which may be able to reduce employee-to-employee transmission (*225*). A cohort study in Singapore estimated that the intervention of enhanced surveillance and segregation of units into smaller working subgroups had significant lower serologically confirmed infections compared to those with standard pandemic plan (17% versus 44%) (*224*). A RCT study evaluated the effectiveness of voluntary waiting at home on full pay measure against influenza A(H1N1)pdm09 transmission in workplaces showed an overall risk reduction by 20% (*107*). Piper et al. (*227*) and Asfaw et al. (*226*) used the resources data from nationally representative survey in the USA, and illustrated that adults with paid sick days had a higher probability of staying at home and hence reduced the face-to-face transmission in workplace.

The remaining 13 studies were simulation studies (*89-91, 228-236*). The 12 simulation studies from the review by Ahmed et al. suggested that the workplace measure alone reduced the cumulative attack rate by 23%, as well as delaying and reducing the peak influenza attack rate (*89, 90, 228-236*). A study in Ottawa suggested that working from home measure combined with other interventions could reduce the illness attack rate from 55% to 8% (*91*).

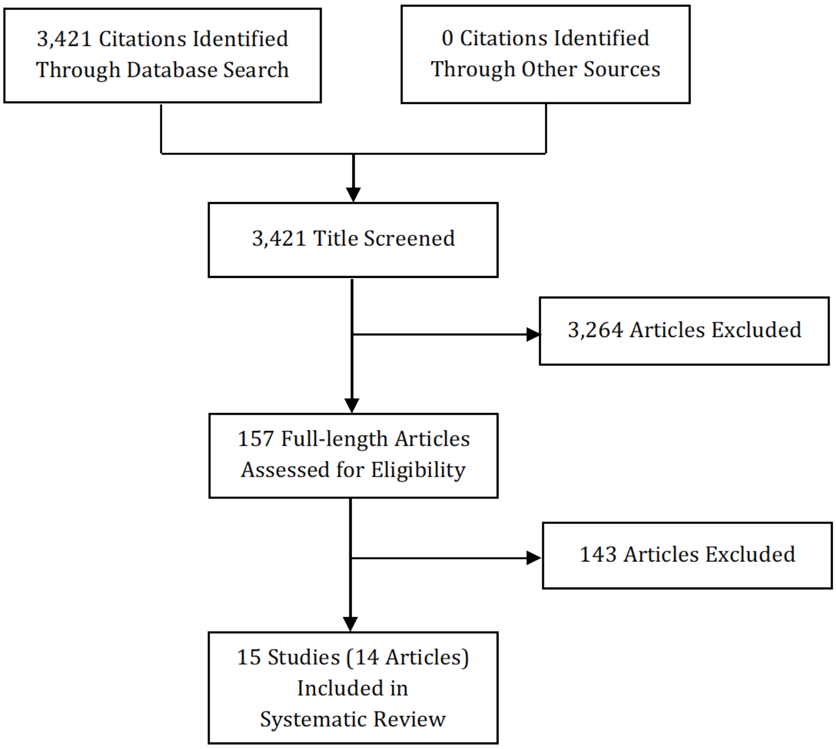


Fig. 21. The flow chart of systematic review by Ahmed

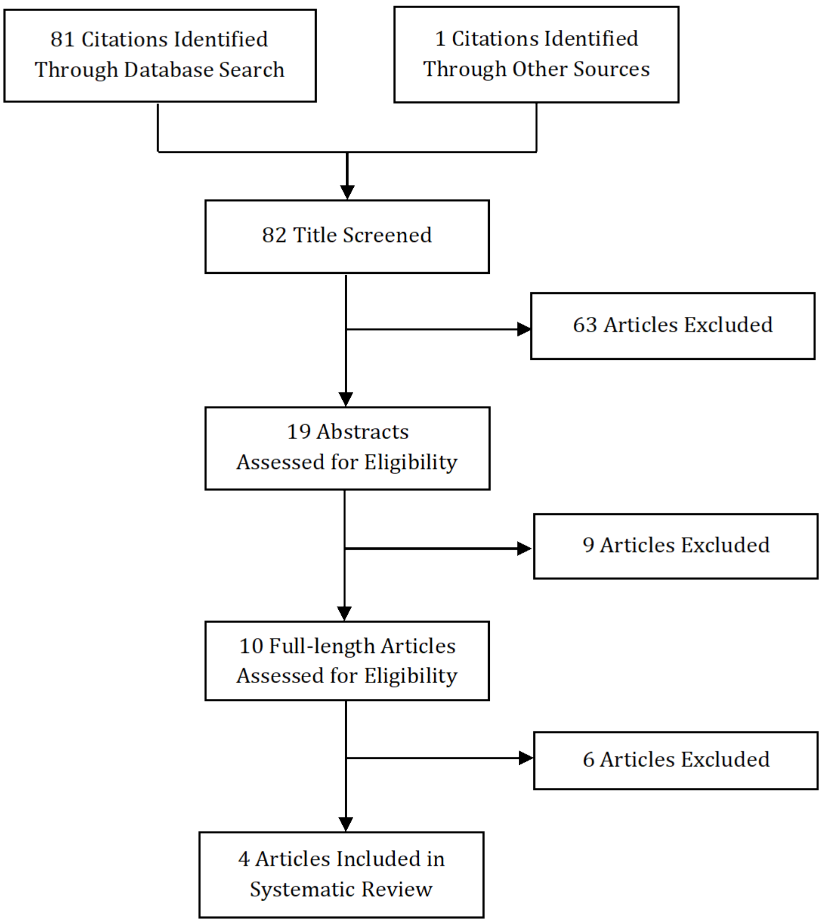


Fig. 22. The flow chart of updated studies in workplace measures

Ethical considerations

Similar to WC, workplace measures could affect the economy and productivity of the society.

Knowledge gaps

A comprehensive review of the ethical issues of workplace measures is lacking, as is a comparison of the benefits and costs of implementing the measures. Other workplace measures have not been studied in depth, such as providing separate studios for people with ILI. In addition, the studies on feasibility and scope of implementation of workplace measures, and the potential impact on families and society transmission are limited.

Table 27. Description of epidemiological studies included in the review of workplace measures

STUDY	STUDY DESIGN	INFLUENZA STRAIN	POPULATION AND SETTING	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Asfaw A, 2017 (*226*)	National representative survey	Influenza A(H1N1)pdm09	71 200 people in the USA	Single: paid sick leave	Employees with paid sick leave have a 32% higher probability of staying at home than workers without paid sick leave, which might reduce the transmission of influenza	Very low
Kumar S, 2012 (*223*)	Cross-sectional study	Influenza A(H1N1)pdm09	Nationally representative sample (n = 2079) of USA	Single: can work from home	The people who unable to work at home were more likely to have had ILI (P< 0.05)	Very low
Lee V, 2010 (*224*)	Cohort study	Influenza A(H1N1)pdm09	Singapore military personnel (n = 437 in control group and n = 470 in intervention group)	Multiple: enhanced surveillance and segregation of units into smaller working subgroups	Confirmed infections were significantly (p< 0.001) lower in intervention group (17%) than in the control group (44%)	Very low
Miyaki K, 2011 (*107*)	Quasi-cluster-RCT	Influenza A(H1N1)pdm09	Two sibling companies (Cohort 1 n = 6634, Cohort 2 n = 8500) in Kanagawa Prefecture, Japan	Single: Voluntary waiting at home on full pay if the family became ILI	The intervention reduced around 20% of overall infection risk in the workplace	Low
Rousculp M, 2010 (*225*)	Cohort study	2007–2008 seasonal influenza	793 employees with ILI in three large US companies	Single: can work from home	Employees who could telework had a 29.7% lower rate of attending work with severe ILI symptoms, which indicated that implement teleworking policies may be able to reduce employee-to-employee transmission	Very low
Piper K, 2017 (*227*)	National representative survey (3 rounds interviews in 2009)	Influenza A(H1N1)pdm09	12 044 employees over 16 years old in the USA	Single: paid sick days	Individuals with paid sick leave are more likely to stay at home in order to reduce the influenza transmission in workplace	Very low

ILI: influenza-like illness; RCT: randomized controlled trial; USA: United States of America.

3.6. Avoiding crowding

Methods

The citations were identified from PubMed, Medline, EMBASE and CENTRAL until 18 October 2018. Two reviewers (SG and ES) screened each title, abstract and article that met the criteria in full. Both epidemiological and simulation studies relative to the effectiveness of avoiding crowding (e.g. cancellation or postpone of events and limitation of attendance) in public area are included. Studies that only report an outbreak event in a crowded area or perceptions on mass gathering but without specific data related to the effectiveness of avoid crowding and studies published in review, letter, news or summary articles were excluded. The effectiveness of cancelling, postponing or limiting attendance in reducing influenza transmission was used when examined the quality of evidence by GRADE.

Results

We identified three studies for the systematic review after reviewing 815 titles and 121 abstracts identified from databases and other sources. The flow chart is shown as Fig. 23. Among these three articles, two of them were based on the 1918 influenza pandemic and one focused on World Youth Day gathering in 2008 (details shown in Table 28).

Hachett et al. and Markel et al. reported a strong association between the early implementation of interventions and the mitigation of pandemic influenza. The study by Markel et al. showed three major categories for NPI: SC, cancellation of public gatherings, and isolation or quarantine in 43 cities in the USA. SC combined with a ban on public gatherings was the most common intervention with a median duration of 4 weeks, which can significantly reduce weekly excess death rate (EDR). Also, early implementation led to greater delays in reaching peak mortality (Spearman $\rho = -0.74$, $P < 0.001$), lower peak mortality rates (Spearman $\rho = 0.31$, $P = 0.02$) and lower total mortality (Spearman $\rho = 0.37$, $P = 0.008$) (*85*). There was a statistically significant association between increased duration of interventions and a reduction in total mortality burden (Spearman $\rho = -0.39$, $P = 0.005$) (*85*). Another study by Hatchett et al. also emphasized the early bans on public gathering, closure public places implementation in reducing the EDR (135). In addition, the basic group accommodation for 1 week during World Youth Day was described by Staff el at. (*237*). People accommodated in a single large place (17.2%) had a significantly higher attack rate compared with people who lived in small classrooms (9.2%) in the context of mass gatherings ($p < 0.01$) (*237*).

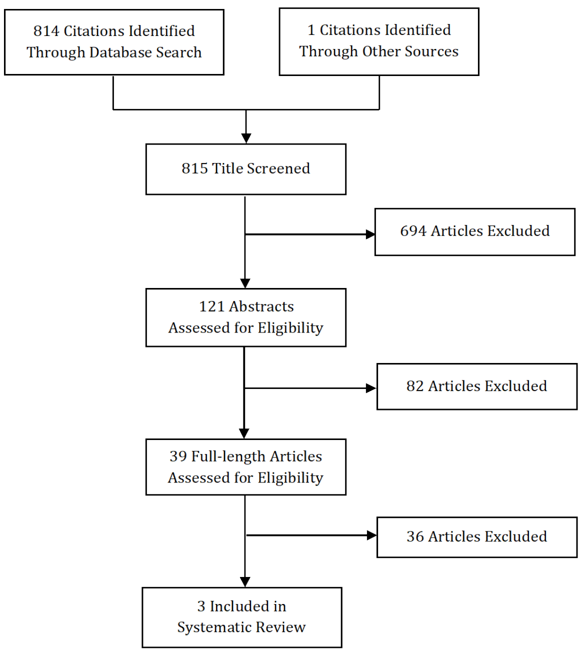


Fig. 23. The flow chart of avoiding crowding

Table 28. Description of studies included in the review of avoiding crowding

STUDY	INFLUENZA	INTERVENTION	OUTCOME	QUALITY OF EVIDENCE
Hatchett RJ, 2007 (*135*)	1918 Pandemic	Early church closure, theatre closure and bans on public gathering	Associated with lower peak excess death rates (Spearman ρ = 0.56, ρ = 0.56, ρ = 0.46 separately)	Very low
Markel H, 2007 (*85*)	1918 Pandemic	Multiple: SC + cancellation of public gatherings + isolation and quarantine.	Implemented earlier and longer duration are significantly associated with the reduction of influenza transmission	Very low
Staff M, 2011 (*237*)	World Youth Day 2008 pilgrims	1 group of pilgrims was accommodated as a large group in a gymnasium and another group was sub-divided into smaller groups and accommodated in classrooms for 1 week.	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%)	Very low

SC: school closure.

Ethical considerations

In urban locations it can be difficult to avoid crowding without considerable social costs. Modification, postponement or cancellation of mass gatherings may have cultural or religious considerations, in addition to public health aspects.

Knowledge gaps

There are still major gaps in our understanding of person-to-person transmission dynamics. Reducing mass gatherings is likely to reduce transmission in the community, but the potential effects are difficult to predict with accuracy. Large-scale RCTs are unlikely to be feasible.

4. TRAVEL-RELATED MEASURES

4.1. Travel advice

Terminology
Travel advice refers to advice from official government to help members of the public to make informed decisions when they are planning to travel, and offer them an objective assessment of risk (*238*). Travel bans are more extreme, and discussed separately. Travel advice can increase travellers' awareness of the travel risk in pandemic countries or areas and may affect decisions to travel.

Methods
The databases including PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating travel advice for influenza in the community setting. Studies had to demonstrate any effectiveness following travel advice to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidences, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening.

Results
A total of 168 records were identified and included in the title and abstract screening, and 146 of the records were excluded. Twelve full-text records were evaluated for eligibility and all were excluded. No full-length articles were included in this systematic review. The flow chart of study selection is shown in Fig. 24.

Ethical considerations
Policy decisions and justification should be open to the public, so that the public awareness of influenza can be increased, and public trust to follow travel advice can be maintained (239).

Regarding the impact for the global economy through the public avoidance of travel or trade, travel advice may develop financial loss of the public (*239*).

Knowledge gaps
There is still no evidence measuring the quantitative effect of travel advice on influenza pandemic, which may hamper the development of policy in this area. Because the outcomes of effectiveness may vary by reproduction number, study of the level of infectivity and travel restriction, influenza strain-specific travel advice can be considered.

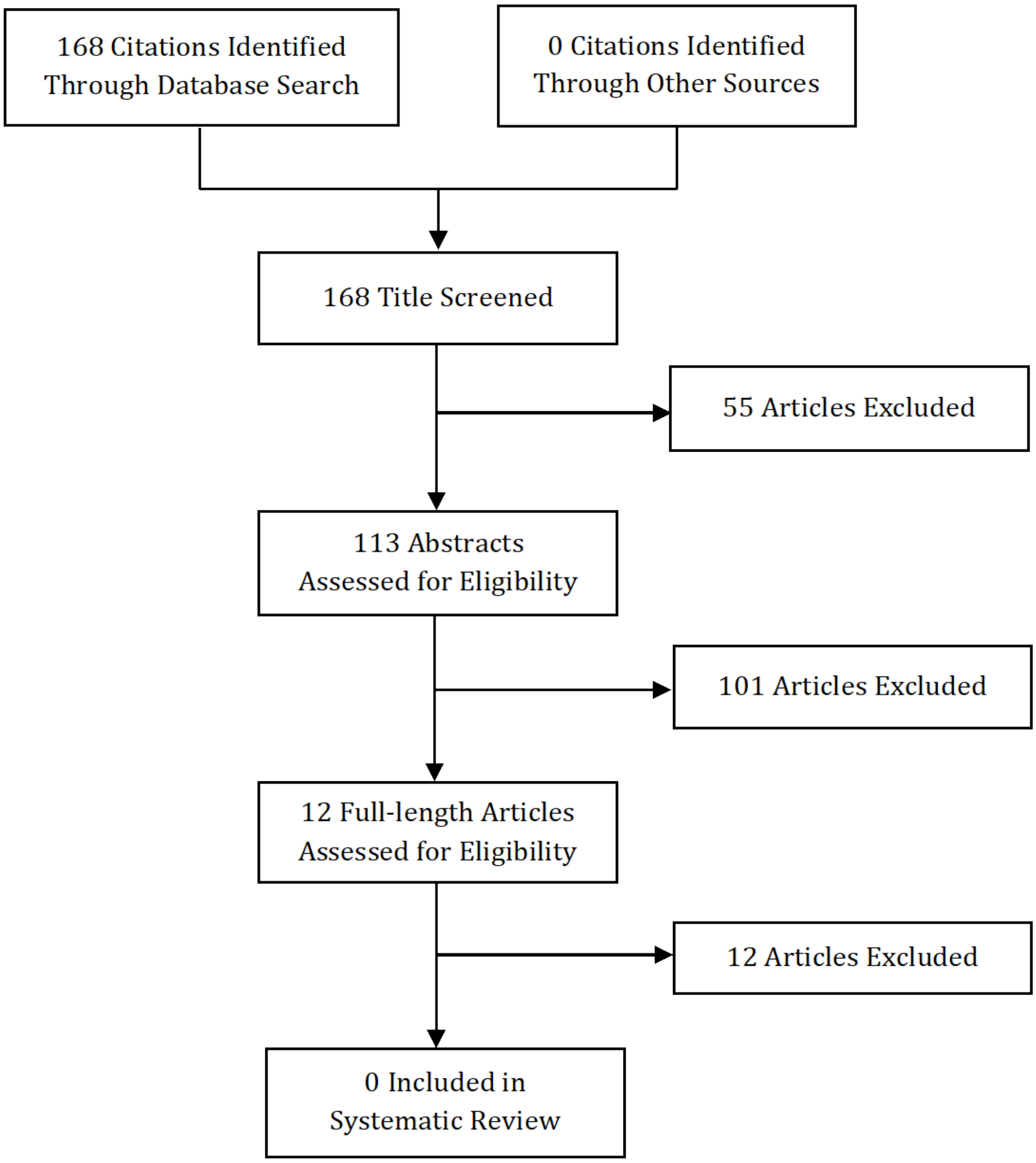


Fig. 24. The flow chart of travel advice

4.2. Entry and exit screening

Terminology

The aim of screening travellers for influenza is to reduce the number of infectious individuals entering or leaving a country. Screening measures include health declarations, visual inspection, and thermography to detect individuals with influenza-related symptoms (*240*). These measures can be conducted at arrival terminal (entry screening) or at departure terminal departure (exit screening) (*241*).

Methods

The databases PubMed, Medline, EMBASE and Cochrane Library were searched until September 2018. Inclusion criteria were primary research evaluating entry and/or exit screening for influenza in the community setting. Studies had to demonstrate any effectiveness following entry and/or exit screening in the community. We excluded studies conducting at health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of entry and exit screening by two independent reviewers.

Results

A total of 297 records were identified and included in the title and abstract screening, and 230 were excluded; 31 full texts were evaluated for eligibility and 19 full texts were excluded. Ten full-length articles were included in this systematic review. A flow chart of study selection shown in Fig. 25. Study details are shown in Table 29, Table 30, Table 31 and Table 32.

A simulation study in the USA estimated that entry screening can detect 50% of infected travellers and is likely to lower the predicted pandemic influenza attack rate by less than 1% (*242*). Furthermore, several simulation studies showed that screening international travellers may help to delay the epidemic by a few days (0–12 days) (*163, 242-244*). However, several observational studies that were conducted at international airports demonstrated that the sensitivity of entry screening was low (5.8% at New Zealand, 6.6% at Japan and 1.1% at USA) (*245-247*), and half of international travel-related case-patients were identified more than a day after arrival by passive case finding and contact tracing in the community, although 37% of international travel-related cases of influenza were screened at the border entry site (*163*). Simulation studies predicted that screening of travellers may not prevent case import and local epidemics (*243*, *244*).

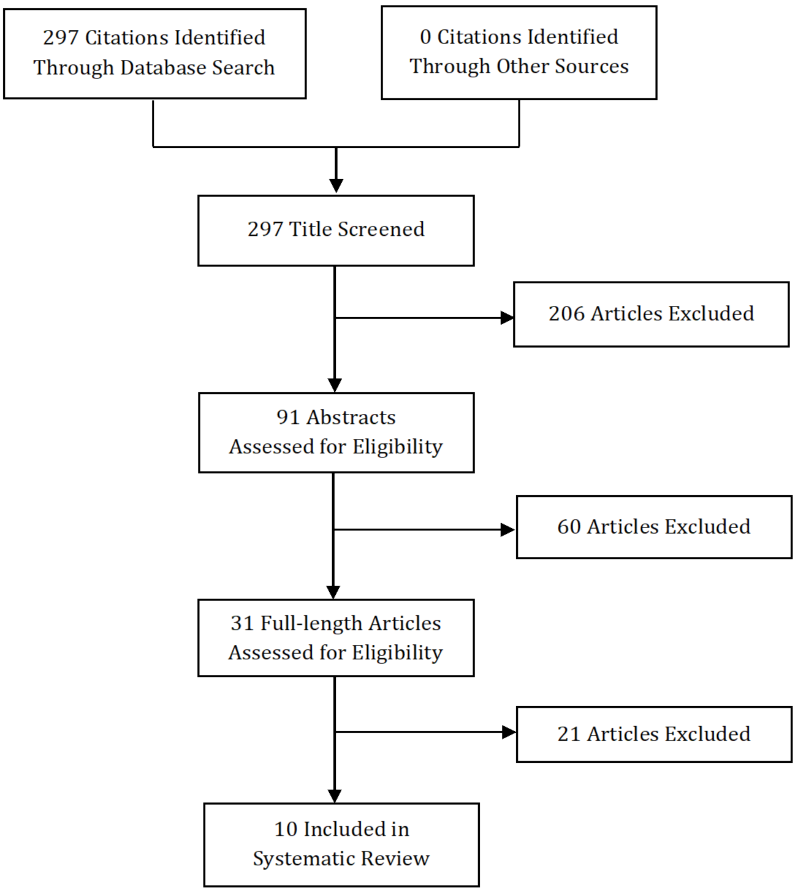


Fig. 25. The flow chart of entry and exit screening

Sensitivity of screening can affect the effectiveness of travellers' screening. One of the major criteria for screening influenza infected travellers is fever, because it is a relatively specific sign of influenza compared with other signs or symptoms. Infrared thermometers have been used for border screening in many locations due to the instantaneous and non-invasive nature. One study showed that the sensitivity and specificity of infrared thermometer were 50.8–70.4% and 63.6–81.7% respectively during influenza A(H1N1)pdm09 in Japan (*248*). An infrared thermal image scanner (ITIS) is another screening tool for the massive number of travellers. A study conducted in New Zealand demonstrated that the sensitivity and specificity of ITIS ranged from 84–86% and 31–71%, respectively (*249*).

Molecular diagnostics can be used, but will be expensive and resource intensive if used in a large population (*250*). Point-of-care antigen detection tests might be more feasible but would still be costly (*250*).

Considering the incubation period of influenza virus infection of 1–2 days (*163*), the variation of symptom presentation and imperfect screening methods (*251*), screening travellers to prevent the introduction of influenza still has limitations. Furthermore, the public health resources including trained staff, screening devices and laboratory resources are limited (247); thus, screening targeted travellers from and to high risk area should be carefully considered.

Although exit screening has been recommended in the past, we did not identify any reports of the actual implementation of exit screening in the literature.

Ethical considerations

Screening should be conducted voluntarily as much as possible, and compulsory screening should be considered very carefully (*239*). Informed consent from the traveller for the screening of specimen-collection including nasal swabs should be obtained in accordance with the International Health Regulations (*252*).

Knowledge gaps

There were no high-quality studies on the effectiveness of entry and exit screening. Quantitative study for the implementation of screening programmes at different times, different combinations, and different pathogens are required to understand the potential advantage of screening (*251*).

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Hale MJ, et al. 2012 (*245*)	• Influenza A(H1N1)pdm09 • R_0 = N/A	• Cross-sectional study • Auckland international airport, New Zealand. • 456 518 international travellers including flight passenger and crew member arriving between 27 April and 22 June 2009	• Entry screening - In-flight announcement - Locator card completion - Travel advisory information - Self presentation	• 409 (0.09%)	• ILI • 109 (27% of medical assessment)	• RT-PCR from 109 respiratory swab	• 4 were positive. • 69 travellers were confirmed as cases passed through airport. • Sensitivity of screening: 5.8% (95% CI: 2.3–14.0%)	• Low sensitivity of entry screening • Mild illness might not see a doctor or did not diagnosed. • The number of cases who passed through the airport was based on estimated fraction of data from the first 100 cases	Very low
Priest PC, et al. 2013 (*247*)	Seasonal influenza	• Cross-sectional study • Christchurch airport, New Zealand. • 23 513 international travellers including flight passenger and crew member arriving between 23 June and 12 September 2008	• Entry screening - In-flight questionnaire (symptoms)	• 1358 (17%)	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties	• Commercial EasyPlex multiplexed tandem PCR kit from respiratory swab No. of Case and non-case:1331 and 2438	• 60 were positive (51, type B; 8, type A; 1 type A&B) • Estimated prevalence: 1.13% (95% CI: 0.77–1.48)	• Either resource intensive or ineffective • Symptom based screening • Not report symptom	Very low
Sakaguchi H, et al. 2009 (*246*)	• Influenza A(H1N1) pdm09; • R_0 = N/A	• Cross-sectional study • Narita airport, Japan • 471 933 international travellers including flight passenger and crew member visited affected countries arriving between 28 April and 18 June 2008	• Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rapid influenza diagnostic test and RT-PCR from 805 respiratory specimens	• 9 were positive. • 141 travellers were found during the community containment measures. • Sensitivity of screening: 6.6%	• Require large amount of human resources • Mild illness travellers were not examined • Not report symptom	Very low
Yu H, et al. 2012 (*163*)	• Influenza A(H1N1)pdm09; • R_0 = N/A	• Retrospective cohort study • China (193 sentinel hospital, 30 provinces) • 7 1 665 persons with confirmed A (H1N1) pdm09 virus between 7 May and 30 November 2009.	• Entry screening – active surveillance at the border and medical monitoring	N/A	• Confirmed case: ARI with laboratory evidence of influenza A(H1N1) pdm09 • ARI: fever (≥ 37.3), and/or recent onset of 1 or more of the following: rhinorrhea, nasal congestion, sore throat or cough	• RT-PCR	• 932 were related to international travel. • 37% of int'l travel-related cases identified at the border. • Half (468/932) were identified 1 or more days after their arrival. • Detection rate of case identified at the entry screening: fever + before arrival: 76%, fever- before arrival 63%	• Epidemic likely delayed by 4 days (100% of screening sensitivity) • Mild illness or subclinical infection might not be examined • Case-based surveillance	Very low

ARI: acute respiratory infection; CI: confidence interval; ILI: influenza-like illness; N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription.

Table 30. Summary of simulation studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	SCENARIO	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Malone JD, 2009 (*242*)	• Pandemic influenza • R0 = 2.4 (Europe), 2.1 (Latin America), and 2.0 (Canada and USA)	• Stochastic discrete event simulation model • 18 US international airport	• Entry screening	• 409 (0.09%)	• 50% of passengers predicted to be infected and high detection rate of 80% for symptomatic travellers for the screening • 100% of passengers infected and 80% of detection rate from screening • 50% of passengers infected and < 50% of detection rate from the screening	• Lowest number of arriving infected passengers (peak day 45–980); attack rate of without and with screening: 30.7% and 30.4% • Peak days 24 and 45 arrive; attack rate of without and with screening: 30.8% and 30.5% • Highest number of arriving Peak day 45–1600 arrive; attack rate of without and with screening: 30.9% and 30.6%	• Entry screening lower the attack rate by less than 1% • Possible variation by airline patterns, screening effectiveness and test accuracy of RT-PCR.	Very low
Cowling BJ, 2010 (*244*)	•R0 = influenza H1N1 N/A	• Bootstrapping • 35 countries had reported to WHO by 6 July 2009 • 100 confirmed cases	• Entry screening - Temperature check prior to disembarkation - Health declaration forms - Observation of symptoms by staffs - Body temperature scan by thermal scanners	N/A	• No screening • a) Medical check before disembarkation • b) Health declaration forms • c) Symptom screening • d) Thermal scanning • e) b) OR c) OR d) • f) b) AND c) AND d)	• Median interval with inter quartile range between first imported case and first local case: 22 days (0, 22days) • a) 21 days (14, 28) • b) 22 days (13, 34) • c) 33 days (7, 41) • d) 22 days (7, 33) • e) 22 days (7, 35) • f) 23 days (9, 35)	• Entry screening did not delay significantly in local transmission • Mild illness or self-limiting nature may affect the result • Did not consider the size of local epidemics.	Very low
Caley P, 2007 (*243*)	• New pandemic influenza •R0 = 1.5, 2.5, and 3.5	• Simulation study • 100% sensitivity for detecting symptomatic infection, • 12 hours of travel	• Exit screening • Entry screening – Screening surface body temperature using infrared thermal scanners	N/A	• Traveller who visited influenza affected countries with 2 symptoms or more of 4 symptoms (1. Nasal discharge or nasal obstruction; 2. Sore throat; 3. Cough; 4. Fever or feeling feverish and chills) or travellers with body temperature > 38°c	• Rate of evading screening: 0.26 (R0 = 1.5), 0.45(R0 = 2.5), 0.59 (R0 = 3.5) • Median delay from 57 to 60 days by screening (R0 = 1.5, 400 travellers / day); natural median delay 57 days * Time delay: the start of an influenza pandemic and its subsequent initiation in other countries	• Delay effect by implementing screening is small compare with natural delay • In-flight transmission not fully considered.	Very low

N/A: not applicable; PCR: polymerase chain reaction; R0: basic reproductive number; RT: reverse transcription; USA: United States of America; WHO: World Health Organization.

Table 29. Summary of epidemiological studies included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Nishiura H, 2011 (*248*)	• Influenza including A(H1N1)pdm09 and other • R_0 = N/A	• Observational study • A) 471 733 travellers including flight passengers and crew members from 28 April 2009 to 18 June 2009 • B) 9 140 435 flight passengers from 1 September 2009 to 31 January 2010	• Entry screening	• a) 805 • b) 1049	• a) (1) contract in Canada, Mexico or USA, or (2) fever ≥ 38°C or 2≥ acute upper respiratory symptoms • b) (a) self-reported symptoms, (2) relatives or friends of (1) or identified by an infrared thermal scanner	• a) RT-PCR from 805 respiratory swab	• a) sensitivity of entry screening: 22% (18/805) • b) sensitivity and specificity of infrared thermal scanners in detecting hyperthermia: 50.8–70.4% and 63.6–81.7%. PPV: 37.3–68.0%	• Fever screening as a sole measure of entry screening is insufficient • Used non-randomized dataset • Confounding factors including age and outdoor temperature should be considered for the performance of infrared thermal scanners	Very low
Priest PC, 2011 (*249*)	Seasonal influenza	• Observational study • Christchurch airport, New Zealand. • 8020 travellers including flight passengers and crew members from 2008	• Entry screening - In-flight questionnaire (symptoms)	• 5274 questionnaires returned • 823 were symptomatic • 1281 were measured temperature using tympanic and ITIS.	• Traveller who reported 1 or more of: cough, sore throat, sneezing, fever or chill, runny or blocked nose, muscle aches or pains, feeling generally unwell, chest discomfort or breathing difficulties.	• MT-PCR	• Sensitivity and specificity of ITIS (84–86% and 42–72%)	• Fever screening using ITIS is insufficient to detect influenza infection • Majority of travellers in this population was afebrile. • Some of infected travellers had anti-pyretic before arrival	Very low

ITIS: infrared thermal image scanner; MT: multiplexed tandem; N/A: not applicable; PCR: polymerase chain reaction; PPV: positive predictive value; R0: basic reproductive number; RT: reverse transcription; USA: United States of America.

Table 32. Summary of studies of PCR assay included in the review

STUDY	INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	NO. OF TRAVELLERS HAD MEDICAL ASSESSMENT	CASE DEFINITION FOR SCREENING AND NO. OF TRAVELLERS MET	LABORATORY TEST FOR THE CASE AND NO. OF SPECIMENS ANALYSED	OUTCOME	COMMENTS AND LIMITATIONS	QUALITY OF EVIDENCE
Chen J, 2018 (*250*)	• Seasonal influenza • R_0 = N/A	• Observational study • Xiamen international airport China • 1 540 076 incoming travellers between May 2015 and May 2016	• Entry screening	• 1224	• ILI (fever≥ 37.5°C, either cough, rhinorrhea, sore throat and/or gastrointestinal discomfort)	• Flu Dot-ELISA • Viral culture	• Sensitivity of Flu Dot-ELISA: 96.6% (95% CI: 92.7–98.7)	• suitable to use rapid influenza test (Flu Dot-ELSIA) • Missed detection of asymptomatic travellers • Sensitivity of viral culture is less than 100%	Very low

ILI: influenza-like illness; PCR: polymerase chain reaction; R0: basic reproductive number.

4.3. Internal travel restrictions

Terminology

Because airports and land transportation are associated with long-distance spread of influenza (*253*), travel restrictions are considered as a measure to reduce regional and international spread (*254*). Although a previous quantitative expert survey study suggests that this travel restriction is likely to be ineffective due to its limited evidence (1), internal travel restriction to prevent domestic travel of persons to influenza is still considered as an NPI.

Methods

The most recent systematic review of travel restriction was published in 2014 by Mateus et al. (*255*). They identified eight studies, which found that internal travel restriction has limited effectiveness and remained unclear. This review included few simulation studies and several reviews of simulation studies, and was intended to measure the overall travel restriction including internal and international restriction. Instead of using this previous review, we conducted a new search in the databases PubMed, Medline, EMBASE and Cochrane Library, until September 2018. Inclusion criteria were primary research evaluating internal travel restriction for influenza pandemic in the community setting. Studies had to demonstrate any effectiveness following internal travel restriction to the public. We excluded studies conducting at the health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating was made for the overall effectiveness of internal travel restrictions by two independent reviewers. The flow chart of study selection is shown in Fig. 26.

Results

At total of 67 records were identified and included in the title and abstract screening, and 56 were excluded; 11 full-text articles were evaluated for eligibility and six of these were excluded; thus, five full-length articles were included in this systematic review. The summary is shown in Table 33.

A time series analysis study conducted in the USA showed that frequency of domestic airline travel is temporally associated with the rate of influenza spread and following September 11 2001, had markedly delayed the epidemic peak 13 days later than the average for other years (*256*). A simulation study predicted that implementation of strict travel restriction (95% travel restriction and enforced for 4 weeks) could reduce the ILI peak by 12% and moderate restriction (50% travel restriction and enforced for 2–4 weeks) could delay the pandemic peak between 1 and 1.5 weeks (127). Another simulation study predicted that more than 80% of internal travel restriction is beneficial (R0 = 1.5; 80% and 99% restriction delayed median days of 22–32 and 52, respectively, until 20 infectious persons arrivals in the designated city) (254). One simulation study estimated that strict internal travel restrictions (90%) could have some impact in delaying the epidemic peak by 2 weeks in the United Kingdom and by less than 1 week in the USA; however, 75% travel restriction would be ineffective (*87*).

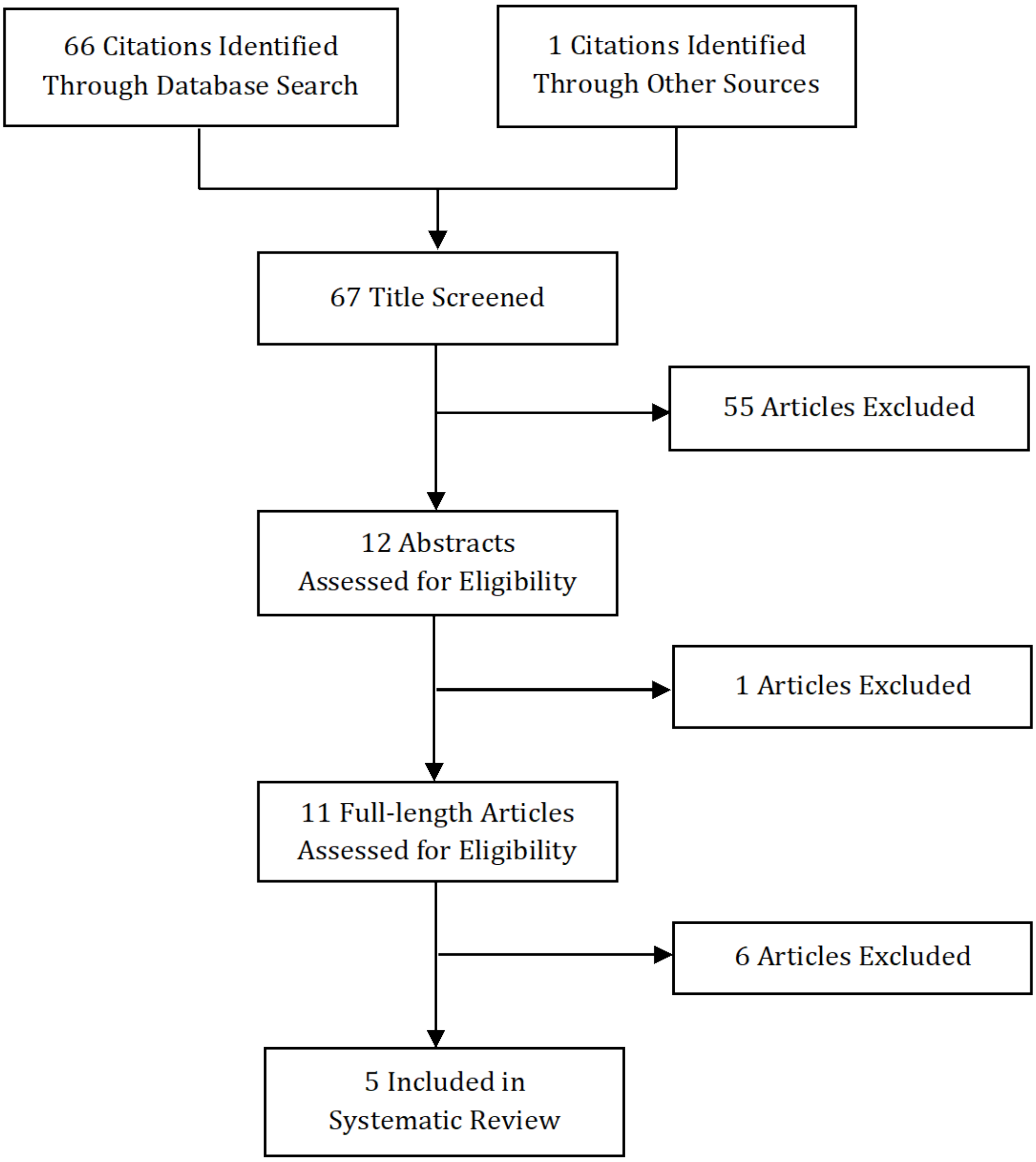


Fig. 26. The flow chart of internal travel restriction

Ethical considerations

Travel restriction should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, governments should pay close attention to adverse economic consequences, particularly on vulnerable populations including workers who have frequent travel and individuals who need to have immediate medical treatment (*239*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• Following September 11 2001, had markedly delayed peak 13 day later than average	• Domestic air travel affects the influenza spread in USA • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very low
Bolton KJ, 2012 (*127*)	• Seasonal influenza • R_0 = around 2	• Stochastic, compartmental patch model of SEIR • Mongolia	• Travel restriction - 50% reduction in mean travel volume in early epidemic	• Delayed the pandemic peak by about 1.5 weeks if maintained for 4 weeks of restriction and by about 1 week if maintained for 2 weeks of restriction • Reduced the attack rates by less than 0.1% when travel volume was reduced by 95%	• Benefit of travel restriction may be limited • Not considered the transmission at the level of household	Very low
Wood JG, 2007 (*254*)	• Seasonal influenza • R_0= 1.5–3.5	• Stochastic SIR model • Australia • Average daily volumes of domestic air travel between Sydney, Melbourne and Darwin	• 80%, 90% and 99% of travel restriction • Median time between the day when the no. infected person first reached 20	• Scenario (Sydney to Melbourne) Beginning of epidemic was delayed in 22–32 days (80% restriction), and 52 days (99% restriction)	• Strict travel restriction required to delay the time • Seasonal variation and further importation of influenza was not considered	Very low
Ferguson NM, 2006 (87)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic mathematical individual-based model • United Kingdom and USA	• Reactive movement restrictions in a 20 km exclusion zone around every case – 75 and 90% restriction • Peak time delay	• Delaying the peak of the epidemic by less than 1 week in USA (without int'l travel restriction) – 90% restriction have some effect on the delaying the peak, but 75% restriction have almost none effect	• Internal travel restriction must be highly strict to have impact • Not considered the effect of personal protective measures on transmission	Very low
Germann TC, 2006 (*257*)	• Seasonal influenza H5N1 • R_0 = 1.6, 1.9, 2.1, and 2.4	• Stochastic agent-based discrete-time simulation model • USA	• 90% of travel restriction	• Epidemic peak delayed few days • 0.2% of increase of cumulative incidence (R_0 = 1.6) • 0.5% of increase of cumulative incidence (R_0 = 1.9)	• The combination of intervention such as social distancing and vaccination may increase the effectiveness of travel restriction	Very low

N/A: not applicable; R0: basic reproductive number; SEIR: susceptible–exposed–infectious–recovered; SIR: susceptible–infectious–recovered; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America.

4.4. Border closures

Terminology
International travel can cause infectious disease cross-border transmission; thus, border closure, one of the measures that can be rapidly implemented, may reduce the epidemic spread of influenza. The transportation of international travel includes ship, bus, train and aeroplane.

Methods
The databases (PubMed, Medline, EMBASE and Cochrane Library) were searched until September 2018. Inclusion criteria were primary research evaluating border closure for influenza pandemics in the community setting. Studies had to demonstrate any effectiveness following border closure in the community. We excluded studies conducted in health care settings, animal-related studies, systematic reviews and/or meta-analysis without updated evidence, not measuring effectiveness of travel advice to the community, and article type of letter, commentary or news. Two reviewers (SR and SG) contributed to the title, abstract and full-text screening. The quality of evidence was measured using the GRADE approach. The rating is made for the overall effectiveness of border closure by two independent reviewers.

Results
A total of 327 records were identified and included in the title and abstract screening, and 314 were excluded; 13 full texts were assessed for eligibility and 11 full-length articles were identified for inclusion in the systematic review. The flow chart of study selection is shown in Fig. 27. The description of the studies shown in Table 34.

An epidemiological study demonstrated that international airline travel could significantly reduce the mortality impact of a pandemic (*256*). Another simulation study estimated that a 99% restriction of border travel between Hong Kong SAR and mainland China may delay the epidemic peak compare with non-travel restriction (sole air restriction, 2 week–delay; both air and land, 3.5 week–delay; all air, land and sea, 12 weeks) (*258*). However, international travel restrictions of other modes of transportation such as land and sea would have less impact (2–3 day delay of the epidemic peak) (*258*). Implementing border crossing travel restrictions within three months of identification of first global case could reduce the seven–month cumulative attack rate by around 2% (*258*). However, implementing travel restrictions after the 5 months of arrival of the first global case would not be expected to be effective (*258*).

Another simulation study reported that international air-travel restriction could delay the peak of epidemic by about 1–3 weeks depending on the transmission rate (1.4, 1.7, or 2) and the level of restriction (90% or 99%), although the attack rate was not significantly affected (*220*). Furthermore, global-scale simulation study reported that travel restrictions could delay the epidemics by about 2 to 3 weeks (*259*) and significantly delay global spread by 5–133 days (*260*).

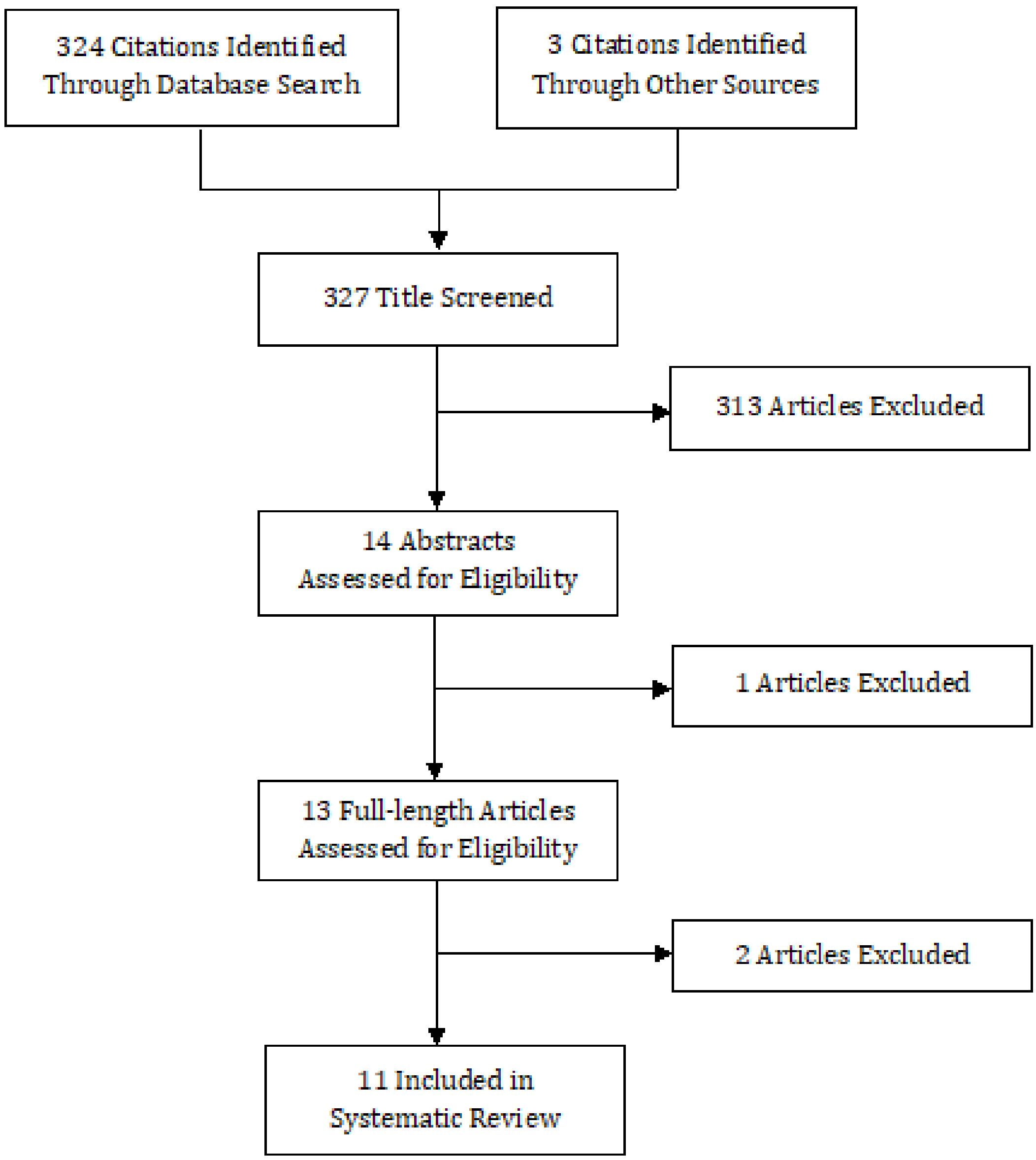


Fig. 27. The flow chart of border closures

A simulation study predicted that 99.9% border control could delay the epidemic peak by 6 weeks (90% and 99% of border control would delay 1.5 and 3 weeks, respectively) (87). Another study estimated that international travel restrictions would slow the importation of cases, and an 80–99% travel restriction would delay of the exportation of cases range 6.6–133 days; however, it did not reduce the magnitude of spread (*261*). Another simulation study predicted that children-selective restriction could be helpful to delay epidemic for a few weeks (*262*).

A simulation study based on travel data from Pacific Island Countries and Territories (PICTs), only six PICTs would be likely to prevent importation of influenza pandemic by 99% of travel restriction through border control. In PICTs, critical necessity such as food and medical supplies are largely dependent on importation, so that strict border closure was carefully considered in PICTs (*263*). Although 99% of travel restriction of all mode of transportation has delayed the epidemic peak, the magnitude of the epidemic was reduced less than 10% in this study. Another observational study in South Pacific Island jurisdictions, during the influenza pandemic which began in 1918, reported that strict maritime quarantine reduced attributable mortality rate from pandemic influenza between 0 and 840 (crude mortality rate per 1000 population) (*99*).

Border closure such as travel restriction is a measure that can be rapidly implemented and it may decelerate the epidemic growth; however, this may not be effective at limiting the magnitude of influenza epidemics (*258*).

Ethical considerations

The human rights of mobility should be considered (*239*). Therefore, as with internal travel restriction, border controls should be voluntarily applied as much as possible, and compulsory intervention should be involved as a last resort (*239*). Furthermore, the stigmatization and discrimination of individuals from influenza affected areas, and economic consequences by implementing border closures should also be considered (*239*, *264*).

Knowledge gaps

Although most of the literature on this topic results from simulation studies and natural experiments, it is unlikely that large trials will ever be done. Improved understanding of transmission dynamics of influenza would be advantageous; for example, on how environmental or other factors can affect influenza transmission and seasonality (*256*).

Table 33. Summary of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Brownstein JS, 2006 (*256*)	• Seasonal influenza • R_0 = N/A	• Time series analysis • USA • Weekly mortality from pneumonia and influenza for 9 influenza seasons (from 1996–1997 to 2004–2005)	• N/A	• September 11 2001 affected international flight volume decreased by 27%, and the peak of influenza mortality was delayed by 2 weeks	• Decrease in travel volume was associated with a delayed and prolonged influenza season. • Study used the data from voluntarily reporting system • Study used influenza mortality time series data which may not correspond to influenza activity	Very Low
Chong KC, 2012 (*258*)	• Influenza H1N1 pandemic • R_0 = 1.4	• Stochastic SEIR model • Hong Kong SAR and mainland China	• Travel restriction – 90%, and 99% travel restriction on different mode transportation (air, land, sea) • Measure the first passage time (first global case onset ~ first local case report)	• 99% of international air-travel restriction delayed the interval between the first imported case and one hundred infected case passed the border by a week and the epidemic peak delayed by two weeks • 99% of restriction of both air and land travel delayed the interval (passage time) by an additional one to two weeks and the epidemic peak delayed about 3.5 weeks • 99% restriction of all mode of transportation delayed the interval by additional 2 months, and delayed the epidemic peak time for about 12 weeks • Travel restriction 3 month after the arrival of first global case reduce the 7-months cumulative attack rate around 2%	• Travel restriction may not be effective • Not considered the infection risk for the out bound susceptible travellers • No adjustment of multi-step journey	Very Low
Ciofi degli Atti ML, 2008 (*220*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global deterministic SEIR model • Italy	• Incoming international flight restriction (90% or 99%)	• Int'l air-travel restriction delayed the interval between first global case report and the importation of the first cases by 7–37 days. Furthermore, the pandemic peak delayed by 6–39 days. The attack rate was reduced less than 0.1%	• Air-travel restrictions can delay 1 to 3 weeks in delaying the epidemic.	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Epstein JM, 2007 (*259*)	• Pandemic influenza • R_0 = 1.4, 1.7, 2.0	• Global influenza transmission model • Global (Hong Kong SAR, London and Sydney)	• Travel restriction (90%, 95%, and 99%) • The interval between the outbreaks occurred in Hong Kong SAR or London and the case-passage time to USA	• First passage time is delayed from 18 days to 31 days (outbreak originated from Hong Kong SAR), and from 7 days to 27 days (from London) with R_0 = 1.7 The delays are larger for smaller R_0	• Air-travel restrictions can delay 2 to 3 weeks in delaying the epidemic. • Model is based on the largest metropolitan areas	Very Low
Cooper BS, 2006 (*260*)	• Pandemic influenza • R_0 = 1.8–5	• Metapopulation model • Global (Hong Kong SAR, London, Sydney)	• Air-travel restriction from affected cities (50, 90, 99 and 99.9%) • Susceptibility (10%, 60%, and 100%)	• Median epidemic peak delay can be ranged between 7–102 days	• Banning flight from affected region would be effective delaying global spread	Very Low
Ferguson NM, 2006 (*87*)	• Seasonal influenza • R_0 = 1.4–2.0	• Stochastic spatially structured mathematical model • USA	• 90, 99% or 99.9% border control in USA	• Imported infections might delay the epidemic peak of USA by 1.5 weeks (90% border control), 3 weeks (99%), and 6 weeks (99.9%)	• Combing travel restriction measure including internal and international have more impact delaying epidemic peak	Very Low
Hollingsworth TD, 2006 (*261*)	• Pandemic influenza • R_0 = N/A • Pandemic influenza	• Simple mathematical SEIR model of an epidemic in a source country with cases exported to other countries	• 80, 99, or 99% of travel restriction • Peak time delay	• The mean time delay exporting the infected case is 5.3 days (80% of restriction), 11.7 days (90%), and 131.7 days (99%)	• Restriction on travel may have limited benefit of global spread of pandemic influenza	Very Low

Table 34. Summary table of studies included in the review

STUDY	STUDY DESIGN INFLUENZA STRAIN INVOLVED AND STRAIN TRANSMISSIBILITY (R_0)	STUDY DESIGN, SETTING AND POPULATION	INTERVENTION AND MEASURE OF INTERVENTION	OUTCOME	COMMENTS AND IMITATIONS	EVIDENCE QUALITY RATING
Eichner M, 2009 (*263*)	• R_0 = 1.5, 2.25, and 3.0	• Probalistic model • PICTs	• 79% or 99% of travel restriction • Assess the probability that an island either occur epidemics or escape the pandemic	• Among 17 PICTs, with 99% travel restriction, six countries (with R_0 = 1.5) and four to five countries (with R_0≥ 2.25) would be likely escaped the pandemic influenza with more than 50% probability. However, with 79% of travel restriction, only one country (with R_0 = 1.5) and no country (with R0≥ 2.25) was likely escaped the pandemic	• Border control can benefit only a few PICTs for avoiding pandemic influenza • Some of data used in this analysis was missing and suboptimal	Very Low
McLeod MA, 2008 (*99*)	• Pandemic influenza • R_0 = N/A	• Epidemiological study • 11 South Pacific Island jurisdictions	• 5–7 days' maritime quarantine • Death rate	• Arrival of pandemic and death rates attributed to influenza per 1000 population was significantly delayed and reduced compare with the other Pacific Island Jurisdiction - American Samoa (1920, no death reported) - Australia (early January 1919, death rate = 2.4) - Tasmania (August 1919, death rate = 0.81) - New Caledonia (1921, death rate less than 11)	• Strict border control in the island can be advantage to delay the pandemic and reduce the mortality • Confounding factors including pre-existing immunity may affect this result	Very Low
Lam ET, 2011 (*262*)	• Pandemic influenza • R_0 = 1.2, 1.6, 2.0	• Simple stochastic model • Hong Kong SAR	• 100% border crossing travel restriction among children	• Children-selective travel restriction delayed the epidemic for a 19–35 days (R_0 = 1.2), and less than 15 days (R_0 = 1.6 and 2.0)	• The intervention was assumed to implemented after pandemic declared	Very low
Bajardi P, 2011 (*265*)	• Pandemic influenza • R_0 = 1.7 with generation interval 3.6 days	• SEIR-like Global Epidemic and Mobility model	• 40% and 90% of int'l travel restriction to and from Mexico	• Mean delay of the arrival of infection from other countries was less than 3 days (40% of restriction), and about 2 weeks (90% of restriction)	• The intervention was assumed to implemented at the early stage of the outbreak (by 3 months)	Very low

N/A: not applicable; PICTs: Pacific Island Countries and Territories; R0: basic reproductive number; SAR: Special Administrative Region; SEIR: susceptible–exposed–infectious–recovered; USA: United States of America.

SUMMARY OF EVIDENCE

Personal protective measures
Personal hygiene measures such as hand hygiene, respiratory etiquette and face masks are widely used as non-pharmaceutical intervention measures to reduce the risk of acquiring or spreading respiratory infections, and for mitigating pandemic influenza. However, our review identified a lack of compelling evidence for the effectiveness of hand hygiene, respiratory etiquette and face masks against influenza transmission in the community. There are still gaps in the evidence base which further research would help to fill.

Environmental measures
Environmental measures including surface and object cleaning are generally conducted to limit the risk of acquiring or spreading respiratory infections within an area. The evidence for the effect of surface and object cleaning on influenza prevention is limited, and no significant reductions in influenza infections were observed by surface and object cleaning intervention; studies provided very low to low quality evidence. Other environmental measures including UV light as air disinfection, ventilation as increasing air change and humidity as amount of water vapour in the air were limited. Therefore, additional research is required to confirm whether these measures could be of value in mitigating pandemic influenza.

Social distancing measures
Social distancing measures including contact tracing, isolation and quarantine of influenza affected individuals, closures of school and workplace, and avoiding crowding reduce the risk of influenza transmission in community settings. Evidence for the overall effectiveness of contact tracing is very limited. Only one study discussed the benefit of adding contact tracing to isolation and quarantine. The addition of contact tracing is estimated to provide at most modest benefit; however, it will increase considerably the proportion of individuals in quarantine. For isolation, currently available evidence showed that even as a single intervention isolation is effective. Compliance of individuals and timeliness of intervention do affect the effectiveness of isolation in mitigation of influenza. Quality of evidence based on GRADE assessment is, however, very low. More robust evidence drawn from epidemiological studies is needed. The effectiveness of quarantine in mitigation of influenza varies. Household quarantine is suggested to be effective in reducing the impact and transmissibility, and in delaying the epidemic peak; the combination of quarantine with other interventions such as case isolation and SC will further strengthen the effectiveness. There is also an increased risk of infection in individuals quarantined concurrently with an isolated individual. Hence, ethical concerns arise for mandated quarantine. Onboard quarantine, on the other hand, has a minimal impact, based on a very low quality of evidence. More robust evidence drawn from epidemiological studies is needed.

SC can reduce the spread of the influenza; however, the threshold for closing time and duration are uncertain. The combination of SC with other interventions is more effective in reducing the spread of infection. Unlike the evidence of effectiveness of SC, evidence on WCs is limited and all six studies for this effectiveness measure were simulation models (i.e. the quality of evidence is very low). Five of these studies suggested that reductions in attack rate, duration of infection or peak numbers occurred because of the WC. The combination with other interventions may enhance the effectiveness of the individual measures. Workplace measures are effective and feasible during a pandemic. Avoiding crowding, which includes separating people into small groups or cancellation of public gatherings, is effective as an intervention in preventing transmission of influenza as well. However, the quality of evidence is very low based on the GRADE approach.

Travel-related measures
Travel-related measures including travel advice, traveller screening, travel restriction and border closures have been used in previous pandemics to limit international spread. The evidence of travel advice against influenza transmission is still uncertain. The effectiveness of screening incoming and/or outbound travellers against influenza spread is also controversial. However, travel restriction and border closure may slow the spread of influenza at the community level, although all the evidence available was of very low quality.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE		RESULTS
1. Hand hygiene	Moderate (lack of effectiveness in reducing influenza transmission)		Eleven RCTs were included in this review. While hand hygiene was not effective against laboratory-confirmed influenza in meta-analysis in community settings and university halls, it was effective in one of two trials conducted in schools.
2. Respiratory etiquette	**None**		No scientific studies were identified for inclusion in this review.
3. Face masks	Moderate (lack of effectiveness in reducing influenza transmission)		Ten RCTs were included in meta-analysis, and there was no evidence that face masks are effective in reducing transmission of laboratory-confirmed influenza.
4. Surface and object cleaning	Low (lack of effectiveness in reducing influenza transmission)		Two RCTs and one cross-sectional study were included in the systematic review. There was evidence that surface and object cleaning could reduce detections of virus in the environment, but there was no evidence of effectiveness against laboratory-confirmed influenza virus infection.
5. Other environmental measures	**UV light**	**None**	No scientific studies were identified for inclusion in this review.
	Ventilation	Very low (effective)	In simulation studies, increasing the ventilation rate reduced influenza transmission.
	Humidity	**None**	No scientific studies were identified for inclusion in this review.
6. Contact tracing	Very low (unknown)		Evidence for overall effectiveness of contact tracing was limited. All included studies were simulation models. Only one study suggested the benefit of adding contact tracing on top of isolation and quarantine. Such addition was estimated to provide at most modest benefit, at the same time this would considerably increase the number of quarantined individuals.

MEASURES	QUALITY OF EVIDENCE	RESULTS
7. Isolation of sick individuals	Very low (effective)	Simulation studies suggested that isolation of sick individuals can reduce transmission in epidemics and pandemics. The overall effectiveness of the measure is moderate and combination with other interventions may improve the effectiveness.
8. Quarantine of exposed individuals	Very low (variable effectiveness)	We identified 6 epidemiological studies and 10 simulation studies eligible for inclusion in our review. Quarantine is generally effective in reducing burden of disease, transmissibility and delaying epidemic peak.
9. SCs	Very low (variable effectiveness)	The effect of reactive SC in reducing influenza transmission varied but was generally limited. Proactive closures and planned school holidays had a moderate impact on transmission. While SCs alone might have an impact, combination with other interventions further improved the effectiveness.
10. WCs	Very low (effective)	The strength of evidence on WC is very low since the identified studies are all simulation studies. Large-scale WCs could delay the epidemic peak for more than one week, and small-scale closures may have a modest impact on attack rate or peak number.
11. Workplace measures	Very low (effective)	The included studies indicated that workplace measures could reduce overall and the peak number of influenza cases, as well as delaying the peak occurrence. While the overall effectiveness and feasibility of workplace measures is modest, combination with other interventions can further improve its effectiveness.
12. Avoiding crowding	Very low (unknown)	Avoiding crowding including separating people into small groups or cancelling public gatherings is an effective intervention to prevent the spread of influenza. However, the effects of measures to avoid crowding in reducing transmission is uncertain.

Table 35. Quality of evidence and summary of results for each NPI

MEASURES	QUALITY OF EVIDENCE	RESULTS
13. Travel advice	**None**	No scientific studies were identified for inclusion in this review.
14. Entry and exit screening	Very low (lack of effectiveness in reducing influenza transmission)	Ten studies were included in this review. Considering the asymptomatic period of infected patients and the sensitivity of screening devices, the effectiveness of screening travellers is likely to be very limited.
15. Internal travel restrictions	Very low (effective)	The effectiveness of internal travel restriction is dependent on the level of restriction, and only very strict restrictions would be expected to have an impact on influenza transmission.
16. Border closures	Very low (variable effectiveness)	Eleven studies were included in this review. Generally, only strict border closures are expected to be effective within small island nations. For island nations, border closure should be carefully considered because it may affect the supply of essential items to the population.

NPI: non-pharmaceutical intervention; RCT: randomized controlled trial; SC: school closure; UV: ultraviolet; WC: workplace closure.

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