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Applied Evidence Synthesis

# What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of seasonal and pandemic influenza?

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**on behalf of UNCOVER Applied Evidence Synthesis**

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**30 July 2023**
Version 2

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# Declarations

## Acknowledgments

This rapid review was carried out by the authors on behalf of the UNCOVER group at the University of Edinburgh. Particular thanks to Dr Madhurima Nundy for representing the group at the WHO conference on RSV and for her feedback, which informed both this review and a sister review on RSV.

## Funding

This rapid review was commissioned from UNCOVER by the World Health Organisation. Professor Evropi Theodoratou is supported by a CRUK Career Development Fellowship (C31250/A22804). Full details of UNCOVER's structure and funding are available on our website (link below). The views expressed in this report are those of its authors and not necessarily those of any funder.

## Authorship Contributions

NA, UB, BL, MR, AZ, MD, EM, RM, ET contributed to the protocol and review design. MD designed and carried out the searches, with input from RM, ET and EM. NA, UB, CD, BL, MR, AZ and EM conducted title & abstract and full-text screening and data extraction. EM led the quality assessment, data synthesis and write-up, with input from NA, UB, BL, MR, AZ, DK, MN, RM and ET.

## Competing Interests

None to declare.

## Open Access Disclaimer



## About UNCOVER

UNCOVER Applied Evidence Synthesis is a group based at the University of Edinburgh which carries out evidence reviews to answer decision-makers' questions about real-world challenges. Originating in the COVID-19 pandemic, UNCOVER now aims to address a broad range of complex issues which have a public health dimension - from emerging diseases to the health effects of climate change - and emphasises collaboration and capacity-building. Find out more at: https://www.ed.ac.uk/usher/uncover.

# What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of seasonal and pandemic influenza?

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## ABSTRACT

**Background**
This review aims to provide an evidence base on key transmission parameters for pandemic and seasonal influenza, to inform the assumptions that decision-makers may use in planning for and managing outbreaks of the disease, including those set out in the World Health Organization (2017) Pandemic Influenza Risk Management [PIRM] guidelines.

Ten parameters of interest are considered: attack rate; secondary attack rate; basic reproduction number (R0); generation time; incubation period; latency period; shedding rate; duration of infectiousness; doubling time; and mode of transmission.

**Methods**
We conducted a rapid review using adapted systematic review methods. Three databases (Ovid MEDLINE, Embase, Global Health) were searched on 5 May 2022, using a pre-defined search strategy, and results were screened by two reviewers using a pre-agreed set of inclusion and exclusion criteria. Data extraction and quality appraisal was conducted by a single reviewer; JBI checklists were used where possible for critical appraisal.

**Results**
The search retrieved 7,979 articles. After screening, 44 studies were eligible for inclusion, providing data on 9 transmission parameters of influenza: attack rate, secondary attack rate (SAR), basic reproduction number ($R_0$), generation time, incubation period, shedding, duration of infectiousness, doubling time and mode of transmission. No studies were found on the latent period of influenza.

The quality of included studies was mostly moderate or good, although the majority of study designs were observational (predominantly cross-sectional), which limits the robustness of the evidence base. Studies covered a wide variety of influenza sub-types (predominantly A(H1N1), A(H3N2) and B, as well as a few studies of human-to-human transmission of A(H7N9)), and a broad range of geographical locations, settings and time periods. This led to considerable variation in findings, limiting our ability to synthesise these into a single coherent set of influenza transmission parameters.

**Discussion**
We analysed the findings of this review against the assumptions set out in Appendix 2 of the PIRM. On the whole, we found that the evidence in this review supports the existing planning assumptions. However, we found that further investigation and development would be useful in respect of: (1) the modes of transmission of influenza; (2) potential planning assumptions in respect of the attack rate and secondary attack rate; (3) differentiating between the infective

period and duration of viral shedding, and better understanding the differences in duration between children and adults; and (4) exploring whether there are significant differences in the patterns of human-to-human transmission of zoonotic influenza viruses, versus those already endemic in humans.

## BACKGROUND

### Context

When planning how to manage the response to an outbreak of infectious disease, decision-makers require information about the basic epidemiological properties of that disease: How fast it is likely to spread within the population; how quickly an infected person will pass it on to their household members; how effectively the infection spreads along different routes of transmission.

Understanding these transmission parameters can help to determine effective infection prevention and control measures to reduce the spread of disease; as well as ensuring that non-pharmaceutical interventions which may involve deprivation of liberty or affect other human rights (such as periods of quarantine or lockdown) are kept proportionate to the known risks.

This review was commissioned in order to update the evidence base supporting the Planning Assumptions in the World Health Organization's (2017) Pandemic Influenza Risk Management guidelines, to help inform ongoing planning for seasonal and pandemic influenza.

### Scope

We prioritised ten parameters of interest: attack rate; secondary attack rate; basic reproduction number (R0); generation time; incubation period; latency period; shedding rate; duration of infectiousness; doubling time; and mode of transmission.

In order to keep the scope of the review manageable within the time available, we did not include clinical attack rate / symptom development as a parameter of interest.

## METHODS

### Protocol

We conducted a rapid review using adapted systematic review methods. We developed a review protocol based on the PRISMA-P statement (Shamseer et al., 2015), which is included as **Appendix 1.**

### Search Strategy

We developed a search strategy by combining search terms related to influenza and disease transmission, combined with concepts to capture studies likely to yield epidemiological data, indexed from 2013 onward. As searches for the current World Health Organization (2017) Pandemic Influenza Risk Management guidelines took place up to 2013, our aim was to identify new evidence published from 2013 onwards.

We carried out searches in three databases: Ovid MEDLINE, Embase and Global Health (CABI). The draft search strategy was adapted to, and piloted in, each database, and searches finalised following feedback from the review team (MD). Search histories for each database are included as **Appendix 2**.

### Screening and Selection of Studies

Search results were deduplicated first using the SR-Accelerator's Deduplicator tool (Institute for Evidence-Based Healthcare). Results were then imported into Covidence (Veritas Health Innovation), where a further automatic deduplication took place before screening began.

We carried out title & abstract screening and full-text screening within Covidence. Each record was independently screened by two reviewers [NA, UB, CD, BL, EM, MR, AZ] against the inclusion and exclusion criteria set out in **Table 1**.

| | **Include** | **Exclude** |
|---|---|---|
| **Population** | Any (human) | Animal studies |
| **Exposure** | Seasonal or pandemic influenza (lab-confirmed) | ILI or SARI<br>Any other virus / condition |
| **Comparator** | N/A | N/A |
| **Outcome** | • Attack rate(s)<br>• Generation interval(s)<br>• Latent period<br>• Incubation period<br>• Duration of infectiousness<br>• Reproduction number<br>• Doubling time / growth rate<br>• Mode(s) of transmission | • Symptomatology<br>• Risk factors for transmission<br>• % symptomatic<br>• Zoonotic transmission [except human-to-human transmission of zoonotic strains] |
| **Study types** | Observational epidemiological studies<br>RCTs and quasi-experimental studies | Case series & case reports<br>Animal studies<br>In-vitro studies<br>Modelling studies<br>Papers with no data (commentaries, etc) |
| **Language** | English | Languages other than English |
| **Setting** | Any | -- |
| **Geographical location** | Any | -- |
| **Timeframe** | Published from September 2013 onwards | Published prior to September 2013 |

***Table 1. Inclusion and Exclusion Criteria for the Review***

### Data Extraction and Management

We created a data extraction form in Microsoft Excel and piloted it on a small number of randomly-chosen studies. Data extraction was carried out by one reviewer for each study [NA, UB, BL, EM, MR, AZ].

We extracted data on study findings, including virus type, parameter of interest (attack rate, secondary attack rate, R0, generation time; incubation period; latency period; shedding rate; duration of infectiousness; doubling time; mode of transmission) and method of measurement or calculation; as well as study characteristics (title, author, publication year, country, setting) and study population information (population size, demographics, vaccination status).

### Quality and Risk of Bias Assessment

In order to appraise the quality of included studies, we used the Joanna Briggs Institute [JBI] checklists for cross-sectional studies, cohort studies, prevalence studies and case-control studies. A full list of the papers included in this review, their study design (for the purposes of quality appraisal) and the overall quality assessment is included in **Appendix 3**. Quality assessment was carried out by one reviewer [EM].

A small number of studies, particularly in respect of the basic reproduction number $R_0$, used a combination of real-world data and statistical modelling to estimate transmission parameters. These studies were not included in the quality appraisal.

### Data Synthesis

As there were not sufficient, comparable data available to support a meta-analysis for any of the included parameters, we conducted a narrative synthesis of findings.

## RESULTS

The literature databases search retrieved 7,979 articles. After screening, 44 studies were eligible for inclusion. The stages of our screening process are set out in the PRISMA diagram in **Figure 1** below.

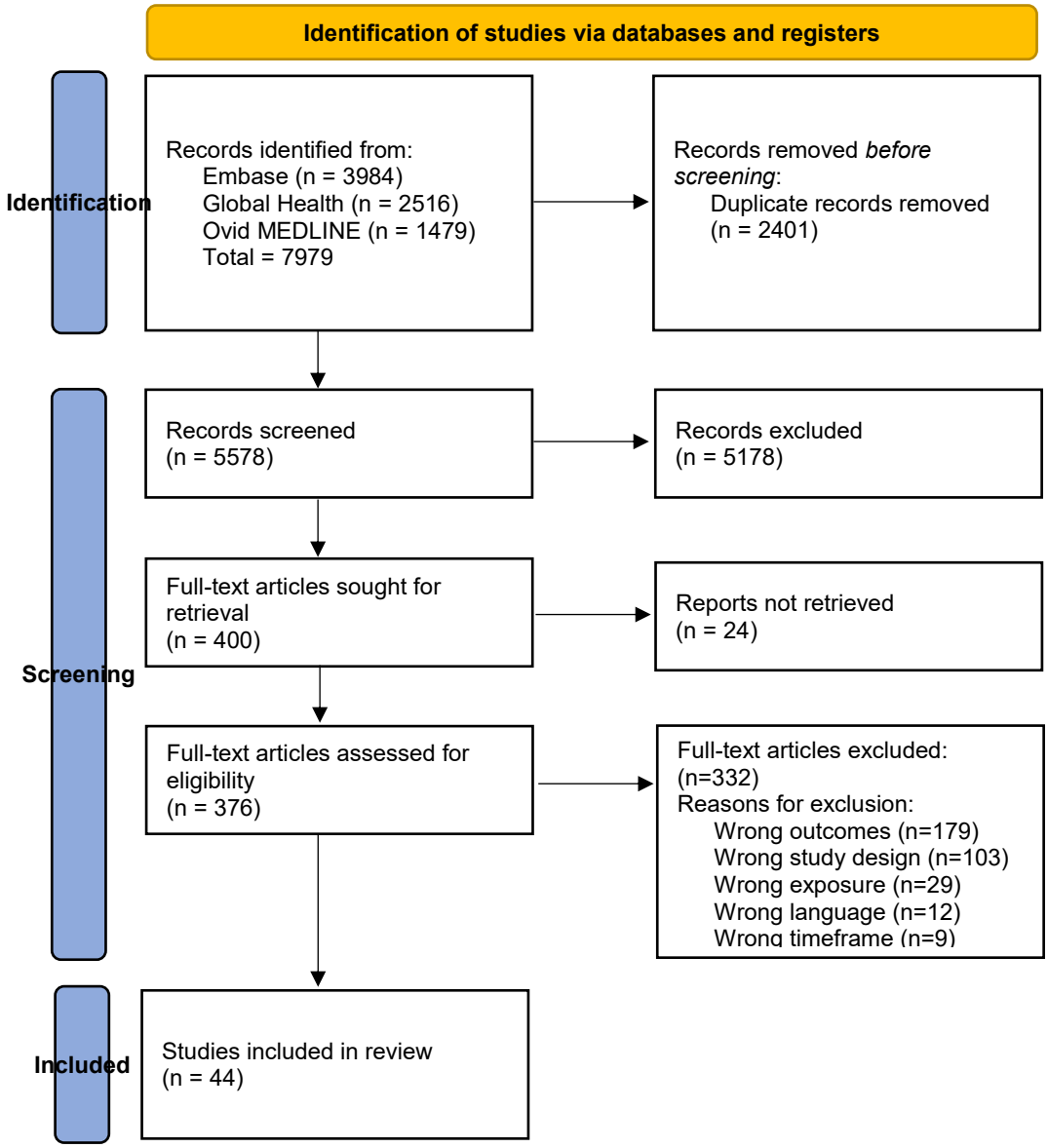



***Figure 1. PRISMA flow diagram***

Of the 44 included studies, **16 reported data on the attack rate** (Chan et al., 2013; Cohen et al., 2021; Dahlgren et al., 2021; Dennis et al., 2020; Eibach et al., 2014; Gurav et al., 2017; Hooshmand et al., 2021; Inglis et al., 2014; Kamigaki et al., 2014; Parkash et al., 2019; Rao et al., 2019; Sansone et al., 2019; Tam et al., 2018; Vera et al., 2014; Wei et al., 2018; Whelan et al., 2016); **11 on the secondary attack rate** (Cohen et al., 2021; Dahlgren et al., 2021; Ip et al., 2017; Iyengar et al., 2015; Levy et al., 2013; Petrie et al., 2013; Saito et al., 2021; Tamò et al., 2022; Thai et al., 2014; Tsang et al., 2015; Yang et al., 2015); **9 on the basic reproduction number ($R_0$)** (Chong et al., 2016; Dávila-Torres et al., 2015; Gurav et al., 2017; Inglis et al., 2014; Liu et al., 2015; Pamaran et al., 2013; White et al., 2014; Yang et al., 2013; Yang et al., 2015); **8 on generation time (serial interval)** (Cohen et al., 2021; Iyengar et al., 2015; Levy et al., 2013; Petrie et al., 2013; te Beest et al., 2013; Thai et al., 2014; Yang et al., 2015; Zhou et al., 2019); **4 on incubation period** (Liu et al., 2021; Saito et al., 2021; Virlogeux et al., 2015; Zhou et al., 2019); **7 on shedding** (Cohen et al., 2021; Ip et al., 2017; Killingley et al., 2016; Lau et al., 2013; Ng et al., 2016; Thai et al., 2014; von Mollendorf et al., 2018); **2 on**

**duration of infectiousness** (Saito et al., 2021; Tsang et al., 2015); **2 on doubling time** (Gurav et al., 2017; Mimura et al., 2015); and **5 (including one modelling study) on mode of transmission** (Fong et al., 2020; Ikonen et al., 2018; Killingley et al., 2016; Xiao et al., 2018; Zhao et al., 2019). Several studies reported data on more than one transmission parameter. A full list of included studies, and the transmission parameters each one relates to, can be found in **Appendix 3**.

We found no studies measuring or calculating the latency period for influenza.

## Attack Rate

**Attack rate** is defined as "the proportion of a group that experiences the outcome under study over a given period (e.g. the period of an epidemic)" with the caveat that "because its time dimension is uncertain or arbitrarily decided, it should probably not be described as a rate" (Porta, 2014). We found 16 studies which aimed to calculate the attack rate of influenza: 6 in healthcare settings, 6 in the community, and 4 in other settings. These studies are described in Table 2 (healthcare), 3 (community) and 4 (other settings) below.

### Healthcare Settings

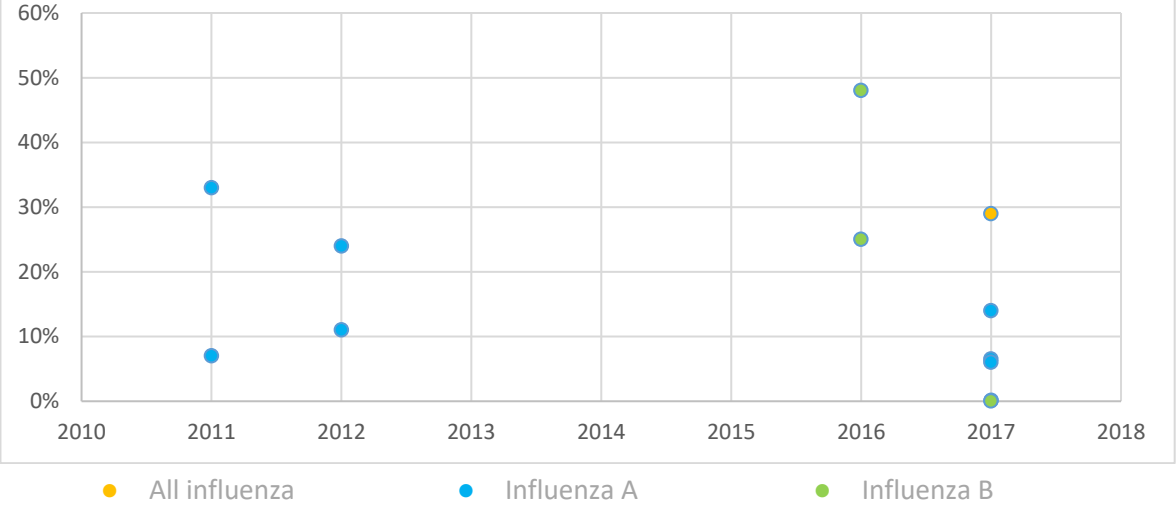
Six studies investigated the attack rate of influenza in healthcare settings (**Table 2**):

**Table 2. Influenza attack rates in healthcare settings**

| Study | Period | Location | Setting | Age range | Sample size | Influenza type | Attack rate | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Hooshmand et al. (2021)** | 2017 | Australia | Care facilities for older adults | Overall: 57-101 years | 38 older adults (F) | A and B | 29% (n=11) | -- |
| | | | | | 124 older adults (G) | A | 14% (n=17) | -- |
| | | | | | 92 older adults (H) | A | 6.5% (n=6) | -- |
| | | | | | 83 older adults (I) | A | 6.0% (n=5) | -- |
| **Chan et al. (2013)** | November 2011 | Hong Kong | Adult psychiatric ward | Mean age 47 (range 34-61) | 21 patients | A/Victoria/ 361/2011-like | 33% (n=7) | -- |
| | | | | | 15 healthcare workers | | 7% (n=1) | -- |
| **Eibach et al. (2014)** | Feb-Mar 2012 | France | Geriatric hospital wards | Mean 88.3 (SD 5.2) | 66 patients | A(H3N2) | 24% (n=16) | -- |
| | | | | Mean 30.2 (SD 10.4) | 57 healthcare workers | | 11% (n=6) | -- |
| **Parkash et al. (2019)** | April – Oct 2017 | Australia | Tertiary hospital | (not given) | 16,112 admissions | A | 0.15% (n=24) | -- |
| | | | | | | B | 0.02% (n=4) | -- |
| **Sansone et al. (2019)** | May 2016 | Sweden | Acute hospital | (not given) | 75 patients | B/Yamagata | 25% (n=19) | -- |
| **Dennis et al. (2020)** | May 2016 | UK | Adult cystic fibrosis centre | Adults (age range not given) | 21 cystic fibrosis in-patients | B/Victoria | 48% (n=10) | -- |

The distribution of attack rates is illustrated in Figure 1 below:

Figure 1. Influenza attack rates by year and influenza sub-type, in healthcare settings




There is considerable variation in attack rates within and between these studies. In one study alone, attack rates varied from 6% to 29% among older adults in care facilities (Hooshmand et al., 2021). While Parkash et al. (2019) report much lower attack rates (0.15% for influenza A and 0.02% for influenza B) than the other studies included here, it is worth noting that these rates are across all hospital admissions (16,112 patients) over the study period; compared to the other studies in this section, which investigated attack rates connected with specific outbreaks.

In studies which compare attack rates between healthcare workers and hospital patients, the attack rates among staff are substantially lower: 33% in patients vs 7% in staff (Chan et al., 2013) or 24% in patients vs 11% in staff (Eibach et al., 2014).

Patients with particular vulnerabilities (beyond age and ill health) appear to have very high attack rates: 33% among patients on an adult psychiatric ward (Chan et al., 2013) and 48% among adults at a cystic fibrosis centre (Dennis et al., 2020). It should be borne in mind that this relates to small overall numbers of patients, and that we cannot say whether these attack rates are significantly higher than those among hospital populations generally. However, this may be an area worthy of further exploration.

**Community Settings**

Six studies investigated the attack rate of influenza in community settings (**Table 3**):

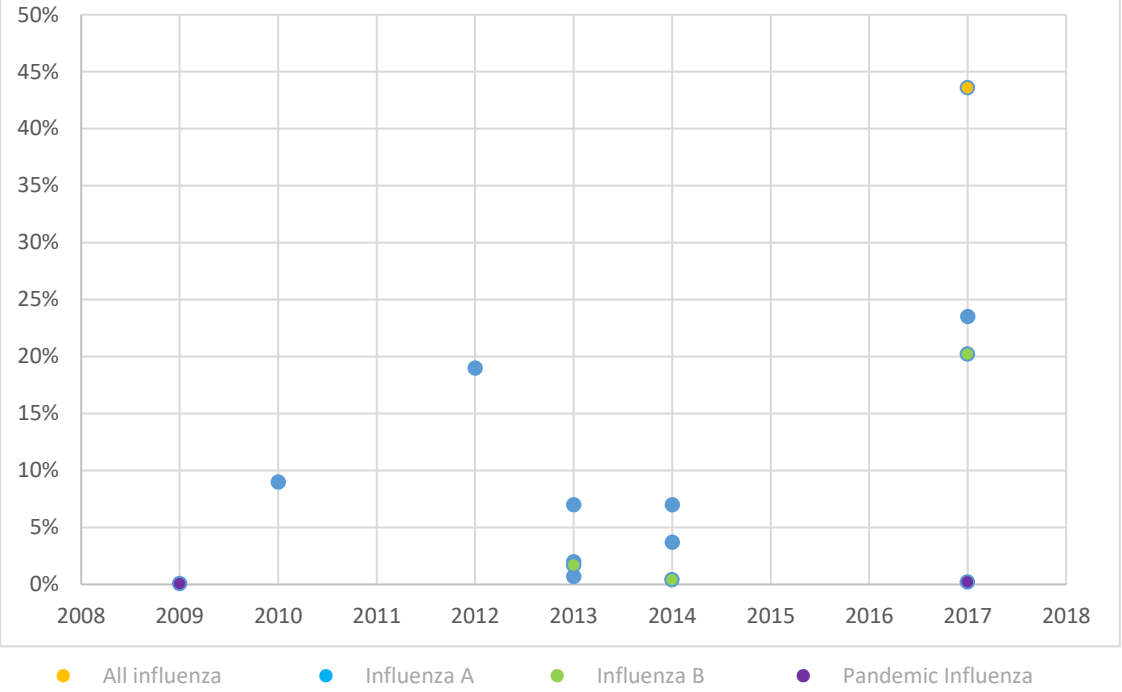
**Table 3. Influenza attack rates in community settings**

| Study | Period | Location | Demographic | Sample size | Influenza type | Attack rate | 95% CI |
|---|---|---|---|---|---|---|---|
| **Inglis et al. (2014)** | April – July 2009 | West Midlands, England | Whole population | N/A | A(H1N1) pdm09 | 56 per 100,000 | 54-58 per 100,000 |
| **Cohen et al. (2021)** | 2017 and 2018 | Agincourt and Klerksdorp, South Africa | Households (all ages) | 81,430 samples from 1,116 people (225 households) | All types | 43.6 per 100 person-seasons | 39.8-47.7 per 100 person-seasons |
| | | | | | A | 23.5 per 100 person-seasons | 20.8-26.6 per 100 person-seasons |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | B | 20.2 per 100 person-seasons | 17.7-23.1 per 100 person-seasons |
| **Dahlgren et al. (2021)** | 2013-2014 | New York City, USA | Households (including at least one child) | 1,144 people | A (H1) | 1.7% | 1.1-2.7% |
| | | | | 1,067 people | A (H3) | 0.7% | 0.4-1.5% |
| | | | | 1,062 people | B | 2.0% | 1.3-3.0% |
| | 2014-2015 | New York City, USA | Households (including at least one child) | 1,088 people | A (H3) | 3.7% | 2.7-5.0% |
| | | | | 1,064 people | B | 0.4% | 0.1-1.0% |
| **Gurav et al. (2017)** | 2012 (weeks 7-15) | Pune, India | Community (Janata Vahasat slum) | 29,797 people | A(H1N1) pdm09 | 0.20% | -- |
| **Rao et al. (2019)** | Jan – Aug 2017 | Dakshina Kannada, India | Whole population | (not given) | A(H1N1) | **>5 years:** 0.42 per 1,000 | -- |
| | | | | | | **5-14 years:** 0.12 per 1,000 | -- |
| | | | | | | **15-29 years:** 0.20 per 1,000 | -- |
| | | | | | | **30-44 years:** 0.34 per 1,000 | -- |
| | | | | | | **45-59 years:** 0.49 per 1,000 | -- |
| | | | | | | **>60 years:** 0.70 per 1,000 | -- |
| **Wei et al. (2018)** | 2010 | Hong Kong | Whole population | 516 people | A(H3N2) | 9% | 4-25% |
| | 2012 | | | 558 people | | 19% | 14-24% |
| | 2013 | | | 619 people | | 7% | 4-10% |
| | 2014 | | | 585 people | | 7% | 4-10% |

The distribution of attack rates is also illustrated in Figure 2 below (although this figure excludes the findings of Rao et al. (2019), as no overall attack rate was given in addition to the age-specific attack rates):

Figure 2. Influenza attack rates by year and influenza sub-type, in community settings




These studies cover a diverse range of rural and urban settings in a number of high-income and low-and-middle-income countries. There is considerable variation in attack rates within and between studies. Cohen et al. (2021) found a particularly high attack rate of 43.6 per 100 person-seasons in South Africa. However, only 24.2 cases per 100 person-seasons had any symptoms, and only 8.6 were symptomatic for influenza-like illness. This study's methods of testing for asymptomatic influenza may contribute to a higher estimate of the attack rate than other studies in this section which relied on symptomatic detection of influenza (Dahlgren et al., 2021; Inglis et al., 2014).

These studies give some indication that attack rate changes by age, with children and older people at higher risk. Cohen et al. (2021) found that incidence was highest in children under 5, and decreased as age increased ($p<0.0001$). Wei et al. (2018) also found that attack rates tended to be higher in children than among adults. Rao et al. (2019) likewise found a higher attack rate among under-5s, initially decreasing with age; but then increasing again, so that the highest attack rate is found among the oldest adults.

**Other Settings**

Four studies investigated the attack rate of influenza in settings which are not either healthcare or community settings, including evacuation centres, military sites and international travellers (**Table 4**). The studies found a wide range of different attack rates, as might be expected given the disparate settings and populations involved:

**Table 4. Influenza attack rates in other (non-healthcare, non-community) settings**

| Study | Period | Location | Setting | Age range | Sample size | Influenza type | Attack rate | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Kamigaki et al. (2014)** | March – April 2011 | Japan | Evacuation centres (post-earthquake) | Mean age 54.4 | 130 (centre A) | A | 7.7% (n=10) | -- |
| | | | | Mean age 51.0 | 702 (centre B) | A | 8.6% (n=60) | -- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean age 50.7 | 606 (centre C) | A | 5.1% (n=31) | -- |
| | | | | Mean age 31.5 | 121 (centre D) | A | 1.7% (n=2) | -- |
| | | | | Mean age 21.5 | 251 (centre E) | A | 0.8% (n=2) | -- |
| **Tam et al. (2018)** | May 2014 – Jul 2015 | Thailand | Army barracks | (not given) | 169 recruits | A or B | 3.4 per 100 person-months | 1.97 – 5.86 |
| **Vera et al. (2014)** | June 2009 | Peru / Ecuador / Costa Rice / USA / Mexico | Peruvian Navy ship | (not given) | 355 crew members | A(H1N1-pdm09) | 22.0% | -- |
| **Whelan et al. (2016)** | Dec 2008 – Sept 2011 | International travel | (Travellers returning to) Netherlands | 18-64 years | 602 travellers | A or B | 15% (n=90) | -- |

### Quality and Generalisability of the Evidence

Study quality was variable overall. The majority of studies were cross-sectional studies, which have a higher inherent risk of bias as study designs, and which were generally of poor to moderate quality as individual studies. There were 3 prevalence studies and 5 cohort studies. Of these, Dahlgren et al. (2021) (from an urban setting in a high-income country) and Cohen et al. (2021) (from urban and rural settings in a middle-income country) are notably of high quality; as is Whelan et al. (2016), although its specific focus on long-term travellers returning to the Netherlands may limit its generalisability to other settings.

Given the considerable variation between studies (in terms of location, setting, study population, virus sub-type, and method of detection) a meta-analysis would not allow for meaningful synthesis of results.

## Secondary Attack Rate

The secondary attack rate is defined as the "number of cases of an infection that occur among contacts within the incubation period following exposure to a primary case in relation to the total number of exposed contacts" (Porta, 2014). We found 11 studies calculating the secondary attack rate of influenza, often analysed by influenza sub-type. The following tables (**Tables 5-10**) present the secondary attack rates grouped by sub-type:

### Table 5. Secondary Attack Rates of Influenza A(H1)

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | 1,946 people in 768 households | A(H1N1) | 25.9% | -- | **Lowest reported SAR = 2.3% (Dahlgren et al., 2021)**<br><br>**Highest reported SAR = 25.9% (Levy et al., 2013)** |
| **Tsang et al. (2015)** | 2008 to 2012 | Hong Kong | Households | 429 exposed contacts | A(H1N1) | 9% | -- | |
| **Ip et al. (2017)** | 2008-2014 | Hong Kong | Households | 2,645 contacts in 852 households | Seasonal A(H1N1) | 2.8% (n=73) | -- | |
| **Iyengar et al. (2015)** | May-Oct 2013 | Klerksdorp and Pietermaritz- | Households | 110 contacts of 30 index cases | A(H1N1) | 17% | -- | |

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| | | burg, South Africa | | | | | | |
| **Dahlgren et al. (2021)** | 2013-2014 | New York City, USA | Households (with at least one child) | 18 households (≥1 case) | A(H1) | 2.3% | 0.3-7.7% | |

## Table 6. Secondary Attack Rates of Pandemic Influenza A(H1)

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | 1,946 people in 768 households | A(H1N1)-pdm09 | 27.1% | -- | **Lowest reported SAR = 1.2% (Ip et al., 2017)**<br><br>**Highest reported SAR = 27.1% (Levy et al., 2013)** |
| **Ip et al. (2017)** | 2008-2014 | Hong Kong | Households | 2,645 contacts in 852 households | Pandemic A(H1N1) | 1.2% (n=33) | -- | |
| **Thai et al. (2014)** | 2009 | Ha Nam province, Viet Nam | Households | 940 people in 270 households – 59 contacts | A(H1N1) pdm09 | 18.6% (n=11) | -- | |
| **Petrie et al. (2013)** | 2010-2011 | Michigan, USA | Households (with at least two children) | 68 exposed contacts | A(pH1N1) | 2.9% (n=2) | -- | |

## Table 7. Secondary Attack Rates of Influenza A(H3)

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | 1,946 people in 768 households | A(H3N2) | 31.6% | -- | **Lowest reported SAR = 0.2% (Dahlgren et al., 2021)**<br><br>**Highest reported SAR = 31.6% (Levy et al., 2013)** |
| **Tsang et al. (2015)** | 2008 to 2012 | Hong Kong | Households | 332 exposed contacts | A(H3N2) | 11% | -- | |
| **Ip et al. (2017)** | 2008-2014 | Hong Kong | Households | 2,645 contacts in 852 households | Seasonal A(H3N2) | 2.6% (n=69) | -- | |
| **Petrie et al. (2013)** | 2010-2011 | Michigan, USA | Households (with at least two children) | 111 exposed contacts | A(H3N2) | 15.3% (n=17) | -- | |
| **Iyengar et al. (2015)** | May-Oct 2013 | Klerksdorp and Pietermaritz-burg, South Africa | Households | 110 contacts of 30 index cases | A(H3N2) | 16% | -- | |
| **Dahlgren et al. (2021)** | 2013-2014 | New York City, USA | Households (with at least one child) | 8 households (≥1 case) | A(H3) | 0.2% | 0.0-6.8% | |
| **Dahlgren et al. (2021)** | 2014-2015 | New York City, USA | Households (with at least one child) | 29 households (≥1 case) | A(H3) | 7.6% | 3.7-13.3% | |

## Table 8. Secondary Attack Rates of Influenza A(H7N9)

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Yang et al. (2015)** | 2013 to 2014 | China | Households | (not given) | A(H7N9) | 1.4% | 0.8-2.3% | -- |

## Table 9. Secondary Attack Rates of Influenza B

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | 1,946 people in 768 households | B | 25.9% | -- | **Lowest reported SAR = 0.3% (Dahlgren et al., 2021)**<br><br>**Highest reported SAR = 25.9% (Levy et al., 2013)** |
| **Ip et al. (2017)** | 2008-2014 | Hong Kong | Households | 2,645 contacts in 852 households | Seasonal B | 1.9% (n=49) | -- | |
| **Petrie et al. (2013)** | 2010-2011 | Michigan, USA | Households (with at least two children) | 91 exposed contacts | B | 7.7% (n=7) | -- | |
| **Saito et al. (2021)** | 2010 to 2016 | Kawasaki, Japan | Households | 2,324 outpatients from 1,807 households | B | 12% to 21% | -- | |
| **Iyengar et al. (2015)** | May-Oct 2013 | Klerksdorp and Pietermaritz-burg, South Africa | Households | 110 contacts of 30 index cases | B | 21% | -- | |
| **Dahlgren et al. (2021)** | 2013-2014 | New York City, USA | Households (with at least one child) | 17 households (≥1 case) | B | 5.3% | 1.5-12.7% | |
| **Dahlgren et al. (2021)** | 2014-2015 | New York City, USA | Households (with at least one child) | 4 households (≥1 case) | B | 0.3% | 0.0-14.3% | |

## Table 10. Secondary Attack Rates of Multiple Influenza Sub-Types (or none specified)

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | 1,946 people in 768 households | All types | 28.2% (n=549) | -- | **Lowest reported SAR = 0% (Tamò et al., 2022)**<br><br>**Highest reported SAR = 28.2%** |
| **Ip et al. (2017)** | 2008-2014 | Hong Kong | Households | 2,645 contacts in 852 households | All types | 8.9% (n=235) | -- | |
| **Petrie et al. (2013)** | 2010-2011 | Michigan, USA | Households (with at least two children) | 267 exposed contacts | All types | 9.7% (n=26) | -- | |
| **Iyengar et al. (2015)** | May-Oct 2013 | Klerksdorp and | Households | 110 contacts of 30 index cases | All types | 19% (n=21) | 12-27% | |

| Study | Period | Location | Setting | Sample size | Influenza type | SAR | 95% CI | Range |
|---|---|---|---|---|---|---|---|---|
| | | Pietermaritz-burg, South Africa | | | | | | |
| **Tamò et al. (2022)** | 2015 to 2017 | Zurich, Switzerland | Tertiary care hospital | 159 contacts with symptomatic cases | A or B | 0.6% (n=1) | 0.02-3.5% | |
| **Tamò et al. (2022)** | 2015 to 2017 | Zurich, Switzerland | Tertiary care hospital | 61 contacts with asymptomatic cases | A or B | 0% | 0.0-5.9% | |
| **Cohen et al. (2021)** | 2017 and 2018 | Agincourt and Klerksdorp, South Africa | Households | 1,088 exposed household members | A or B | 10% (n=109) | 9-13% | |

Cohen et al. (2021) found that transmission was highest from index cases with two or more symptoms (secondary attack rate of 17% (95% CI 14-21%)) and lowest from asymptomatic cases (6% (95% CI 4-8%)). Nevertheless, asymptomatic index cases were responsible for about a quarter of all secondary cases. Thai et al. (2014) found a positive association between secondary infection risk and the index case having a wet cough, only (OR 1.36 (95% CI 1.07-1.72), p=0.012).

Iyengar et al. (2015) found that the secondary attack rate was much higher in households with an index case under the age of five: 30%, compared to 17% in households with an index case aged over five (p=0.17). By contrast, Petrie et al. (2013) found no significant variation in secondary transmission risk based on the age of the index case.

In terms of influenza sub-type, Levy et al. (2013) and Iyengar et al. (2015) found no significant difference between the overall secondary attack rate and the rates by sub-type. Saito et al. (2021) reported a higher range of secondary attack rates for Influenza A (20-32%, depending on household size) than Influenza B (12-21%).

Only one study (Tamò et al., 2022) looked at secondary transmission in a hospital rather than a household setting. Notably, this study used phylogenetic analysis to explore the relationship between participants' influenza strains. Initially, based on PCR results and contact tracing, the study identified seven possible clusters of secondary transmission, involving multiple people. Following phylogenetic analysis, this was reduced to one single transmission event. This may suggest that, in studies without this additional level of analysis, the role of secondary transmission may be over-estimated. However, further studies would be needed to confirm this.

**Quality and Generalisability of the Evidence**

The quality of these studies was generally high, although limited by study design (nine studies were effectively cross-sectional, and two were cohort studies). The studies covered a diverse range of geographical areas in high-income and low-and-middle-income countries, including urban and rural settings. Almost all studies took place in household settings, and several studies required the presence of at least one child in the house – so, to the extent that there is an association between age and transmission of influenza, this may lead to an overestimation of the secondary attack rate compared to the general population.

## Basic Reproduction Number (R0)

The basic reproduction number is "a measure of the number of infections produced, on average, by an infected individual in the early stages of an epidemic, when virtually all contacts are susceptible"

(Porta, 2014). It is an epidemiologic metric used to describe the contagiousness or transmissibility of infectious agents in a population (Delamater et al., 2019). We found nine studies which aimed to calculate the $R_0$ of influenza, each outlined in Table 11 below.

**Table 11. Estimates of the Basic Reproduction Number ($R_0$) of Influenza**

| Study | Notes | Influenza type | Period | Location | R0 (95% CI) |
|---|---|---|---|---|---|
| **White et al. (2014)** | Modelled based on close contacts only | H1N1 | 2009 | South Africa | 0.96 (0.75-1.58)* |
| | Modelled based on all physical contacts | | | | 0.92 (0.71-1.51)* |
| **Inglis et al. (2014)** | -- | H1N1 | 2009 | UK | 1.43 (1.34-1.52) |
| **Yang et al. (2013)** | Bettencourt method | H1N1 | 2009 | China | 1.05 (0.04-2.71) |
| | Kelly method | | | | 1.46 (0.10-2.87) |
| **Pamaran et al. (2013)** | Using mean generation time: 2.6 days | H1N1 | 2009 | Philippines | 1.14 (1.13-1.15) |
| | Using mean generation time: 4 days | | | | 1.09 (1.08-1.10) |
| | Using mean generation time: 2.6 days | H1N1 | 2010 | Philippines | 1.09 (1.08-1.10) |
| | Using mean generation time: 4 days | | | | 1.06 (1.05-1.07) |
| **Gurav et al. (2017)** | -- | H1N1 | 2012 | India | 1.30 (not given) |
| | -- | | 2015 | | 1.64 (not given) |
| **Liu et al. (2015)** | -- | H1N1 | 2009-2013 | China | 1.82 (not given) |
| **Dávila-Torres et al. (2015)** | -- | H1N1 | 2013-2014 | Mexico | 1.23 (1.20-1.26) |
| **Yang et al. (2015)** | -- | H7N9 | 2013-2014 | China | 0.08 (0.05-0.13) |
| **Chong et al. (2016)** | -- | H7N9 | 2013-2015 | China | 0.27 (0.14-0.44) |

*presented range

Seven of the studies estimated $R_0$ for influenza A(H1N1). With the exception of White et al. (2014), studies consistently found the $R_0$ of influenza A(H1N1) to be >1, both during the pandemic year (2009) and subsequently. The range of $R_0$ values found for influenza A(H1N1) varied from 0.92 (95% CI 0.71-1.51) to 1.82 (95% CI not given).

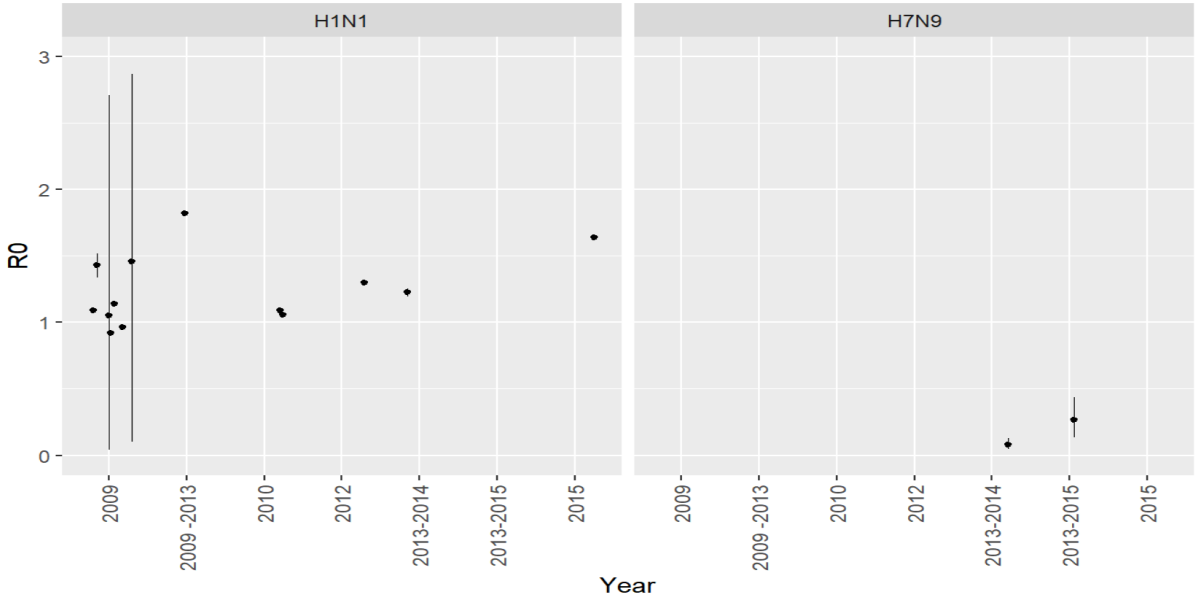
To calculate $R_0$, studies applied a variety of statistical modelling methods to real-world data from particular outbreaks. Different approaches included modelling based on close contacts only versus

all physical contacts (White et al., 2014); modelling using different mean generation times (Pamaran et al., 2013); and using different statistical methods (Yang et al., 2013).

Of the two studies which estimated $R_0$ for human-to-human transmission of avian influenza A(H7N9) (Chong et al., 2016; Yang et al., 2013), both found $R_0$ to be substantially less than 1 – ranging from 0.08 (95% CI 0.05-0.13) to 0.27 (95% CI 0.14-0.44).

Figure 3 below shows the range of $R_0$ values found, by year and influenza sub-type.

**Figure 3. Basic Reproduction Number of Influenza, by Sub-type and Year**




**Quality and Generalisability of the Evidence**

Only studies which used some real-world data in order to estimate $R_0$ were included in this review – pure modelling / simulation studies were excluded. Overall, the evidence base is fairly limited, with seven studies providing estimates for influenza A(H1N1) and two for A(H7N9); no studies on the $R_0$ of A(H3N2) or influenza B were found. We did not carry out a quality appraisal of the modelling studies included in this section of the review.

It is essential to interpret and apply $R_0$ values with a caveat. $R_0$ is multifactorial and is not a biological constant for a pathogen. It can have dissimilar values during different epidemics of the same virus (Froda & Leduc, 2014). It is affected by the environmental factors and behaviour of the infected population as well as pathogen characteristics. Simple SIR or SIRS models are at risk of underestimating the $R_0$ values as it has been shown that models that account for age structure tend to produce higher estimates of $R_0$ (Pitzer et al., 2015; Weber et al., 2001; White et al., 2007)

$R_0$ is rarely measured directly and is commonly calculated using modelling strategies. The $R_0$ values are, therefore, greatly dependent on the model structure and assumptions. Although $R_0$ is a widely used metric in the infectious disease epidemiology field, it is essential to note that the application of $R_0$ outside the region where it was calculated is limited (Ridenhour et al., 2014).

In addition, $R_0$ applies to a population only when the entire population is susceptible to the disease – i.e. when no one is vaccinated or has had the disease before, or there is no means of controlling the disease spread. A combination of these conditions very rarely occurs in the case of influenza, as population vaccination campaigns are common, and non-pharmaceutical interventions have been

found to be effective in controlling the spread. The effective reproduction number, therefore, may be more relevant in the case of influenza, as it measures the expected number of new infections caused by an infectious individual in a population where some individuals may no longer be susceptible to infection (Gostic et al., 2020).

## Generation Time

The **generation time**, or **serial interval**, is "the period of time between analogous phases of an infectious illness, in successive cases of a chain of infection, that is spread from person to person" (Porta, 2014). We found eight studies which calculated the serial interval of influenza, each outlined in Table 12 below.

**Table 12. Estimates of the Serial Interval of Influenza**

| Study | Period | Location | Setting | Age range | Sample size | Influenza type | Serial interval | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **te Beest et al. (2013)** | June 2009 | Netherlands | Community | 1-69 years | 74 cases in 16 clusters | A(H1N1) | 2.6 days | 2.2-3.2 |
| **Cohen et al. (2021)** | 2017 and 2018 | Agincourt and Klerksdorp, South Africa | Households | All ages | 1,088 exposed household members | A or B | 5.9 days | *SD 2.6* |
| **Iyengar et al. (2015)** | May-Oct 2013 | Klerksdorp and Pietermaritz-burg, South Africa | Households | All ages | 8 contact pairs | A or B | 2.1 days | *SD 0.35, range 2-3 days* |
| **Levy et al. (2013)** | 2008-2010 | Bangkok, Thailand | Households | All ages (index cases all children) | 251 index cases and 315 infected contacts | All types | 3.3 days | -- |
| | | | | | | A(H1N1) pdm09 | 3.1 days | *SD 1.4* |
| | | | | | | A(H1N1) | 3.3 days | *SD 1.9* |
| | | | | | | A(H3N2) | 3.5 days | *SD 1.9* |
| | | | | | | B | 3.7 days | *SD 2.0* |
| **Petrie et al. (2013)** | 2010-2011 | Michigan, USA | Households (with at least two children) | All ages | 30 secondary cases | All types | 3.2 days | 2.4-3.9 |
| | | | | | 17 secondary cases | A(H3N2) | 2.5 days | 1.8-3.3 |
| | | | | | 5 secondary cases | A(pH1N1) | 2.8 days | 1.3-5.0 |
| | | | | | 8 secondary cases | B | 4.9 days | 3.3-6.3 |
| **Thai et al. (2014)** | 2009 | Ha Nam province, Viet Nam | Households | All ages | 18 index cases | A(H1N1) pdm09 | 2 days | *Range 1-3 days* |
| **Yang et al. (2015)** | 2013 to 2014 | China | Households | All ages | (not given) | A(H7N9) | 9.4 days | -- |
| **Zhou et al. (2019)** | 2013 to 2017 | China | Community | All ages | 14 secondary cases | A(H7N9) | 9 days | *Range 6-11 days* |

The range of reported serial intervals varies from **2.0 to 5.9 days**, with the exception of two studies of human-to-human transmission of avian influenza A(H7N9), which reported much longer serial intervals of around 9 days (Yang et al., 2015; Zhou et al., 2019).

Studies examined possible causes of variation in the serial interval. Cohen et al. (2021) suggested that the high proportion of asymptomatic and mild cases in their study led to the finding of a longer serial interval (5.9 days). te Beest et al. (2013) explored different settings, finding shorter generation intervals in households (2.1 days, 95% CI 1.6-2.9) and camps (2.3 days, 95% CI 1.4-3.4) than in workplaces (2.7 days, 95% CI 1.9-3.7) and schools (3.4 days, 95% CI 2.5-4.5) – however, they suggest

that under-reporting is more likely in schools, possibly leading to an overestimate of the generation time. Levy et al. (2013) found variation by age of index cases and contacts.

Levy et al. (2013) and Petrie et al. (2013) found that the serial interval for Influenza B was significantly longer than that for Influenza A sub-types, although this varied from half a day to two days longer.

**Quality and Generalisability of the Evidence**

There was one cohort study and seven cross-sectional studies. Studies were generally of a high standard, with the exception of the studies related to influenza A (H7N9), which contained much less detailed and transparent information about their methods.

## Incubation Period

The **incubation period** is "the time interval between invasion by an infectious agent and appearance of the first sign or symptom of the disease in question" (Porta, 2014). We found four studies on the incubation period of influenza, each outlined in Table 13 below.

**Table 13. Estimates of the Incubation Period of Influenza**

| Study | Period | Location | Setting | Age range | Sample size | Influenza type | Incubation period | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Liu et al. (2021)** | 2020 (Jan-Feb) | China | Hospital | (not given) | 41 patients | A or B | 1.4 days | 1.3-1.5 |
| **Saito et al. (2021)** | 2010 to 2016 | Kawasaki, Japan | Households | All ages | 2,324 outpatients from 1,807 households | A | 1.43 days | 0.03-5.32 |
| | | | | | | B | 1.66 days | 0.21-4.61 |
| **Virlogeux et al. (2015)** | 2013 to 2014 | China | Community | (not given) | 229 people | A(H7N9) | 3.4 days | 3.0-3.7 |
| **Zhou et al. (2019)** | 2013 to 2017 | China | Community | All ages | 14 secondary cases | A(H7N9) | 4 days | *Range 1-12* |

The range of reported mean incubation periods ranges from **1.4 to 4 days**, with higher estimates for avian influenza A(H7N9) than for other sub-types of influenza.

Virlogeux et al. (2015) seek to model the distribution of incubation periods for influenza A (H7N9). For public health purposes, they recommend not only focusing on the mean incubation period, but also the 95$^{th}$ percentile (which they calculate as 6.5 days; 95% CI 5.9-7.1 days). They suggest that this additional measurement might be used to determine the period of observation for potentially exposed persons.

**Quality and Generalisability of the Evidence**

Study quality overall was variable, with some moderate and some poorer quality studies, all cross-sectional in design. It should be noted that half the studies in this section focus on human-to-human transmission of avian influenza A(H7N9), which appears to have a longer serial interval (see previous section) and incubation period than other forms of influenza. These studies should perhaps be taken separately from studies of other influenza sub-types, to avoid potentially skewing the results.

## Shedding

We take **shedding** to mean the excretion of virus particles from the body via any bodily route. Shedding is sometimes taken as a proxy for infectivity, for example when determining periods of isolation or quarantine; but this is not necessarily accurate, as studies have found that viral shedding

can still be detected even when the virus that has been shed is no longer viable (Tsang et al., 2015; Widders et al., 2020).

We found four studies on the duration of viral shedding, outlined in Table 14 below, together with one further study which compared viral shedding duration between children and adults (Ng et al., 2016); and two studies which explored the volume of virus shed (Ip et al., 2017; Lau et al., 2013).

**Duration of Shedding**

**Table 14. Estimates of the Duration of Viral Shedding of Influenza**

| Study | Period | Location | Setting | Sample | Influenza type | Average duration of shedding | Range / prolonged shedding | How measured? |
|---|---|---|---|---|---|---|---|---|
| **Cohen et al. (2021)** | 2017 and 2018 | Agincourt and Klerksdorp, South Africa | Households | 1,088 exposed household members | A or B | 6.5 days | IQR 3-10 days | Nasopharyngeal swabs tested with real-time RT-PCR |
| **Killingley et al. (2016)** | 2009 to 2011 | England | Hospitals and community settings | 42 patients with confirmed influenza | A(H1N1) pdm09 | 6.2 days | IQR 5-7 days; range 2-15 days | As measured by PCR |
| | | | | | | 4.6 days | IQR 4-5 days; range 3-10 days | As measured by viral culture |
| **von Mollendorf et al. (2018)** | 2012 to 2014 | South Africa | Community | 264 participants | All types | 7 days | IQR 3-11 days | rRT-PCR of naso- and oropharyngeal swabs |
| **Thai et al. (2014)** | 2009 | Ha Nam province, Viet Nam | Households | 18 index cases | A(H1N1) pdm09 | 6.0 days | IQR 4.0-7.0 days | Swabs tested with RT-PCR |
| | | | | 6 secondary cases | A(H1N1) pdm09 | 6.5 days | IQR 6.0-8.8 days | |
| | | | | 5 asympto-matic cases | A(H1N1) pdm09 | 6.0 days | IQR 4.0-7.0 days | |

Overall, these studies give a fairly narrow range for mean duration of shedding, from **4.6 to 7 days**.

A fifth study, by Ng et al. (2016), is not included in the table above because mean overall shedding duration is not provided. However, the study focused on comparisons of viral shedding between children and adults, and had two important findings:

- Shedding duration in children is longer than in adults – this finding is also supported by Cohen et al. (2021) and von Mollendorf et al. (2018), although Killingley et al. (2016) found no significant difference in duration.
- Children (but not adults) tend to begin viral shedding before symptoms start to show: Ng et al. (2016) found that viral shedding began before symptom onset for children aged 0-5 (mean -1.1 days; IQR -2.3, 0.4 days) and 6-15 years old (mean -1 day; IQR -2.2, 0.5 days), but not for people aged 16 and over (mean 0.2 days, IQR -1.2, 2.3 days).

Thai et al. (2014) also found evidence of presymptomatic shedding, in 3 out of 6 symptomatic secondary cases (ages not given).

Symptomatic illness is also associated with a longer duration of shedding (Cohen et al., 2021). von Mollendorf et al. (2018) examined the relationship between HIV status and influenza viral shedding, and found no significant difference between HIV-infected and uninfected people. However, they did find that immunocompromised, HIV-infected people (with low CD4 counts) were more likely to shed

for longer (adjusted hazard ratio 3.55, 95% CI 1.05-12.08), leading to a greater risk of ongoing transmission or possible viral evolution.

**Volume of Shedding**

Ip et al. (2017) compared the volume of shedding between people with symptomatic, paucisymptomatic and asymptomatic influenza. For people with influenza A(H1N1)pdm09, A(H1N1) and B, mean levels of viral shedding were approximately 1-2 $\log_{10}$ copies lower among pauci- or asymptomatic cases than among symptomatic cases (for influenza A(H3N2), the levels were similar among all patients). Thai et al. (2014) also found that peak and day two viral loads were higher among symptomatic than asymptomatic participants.

Lau et al. (2013) investigated variation in viral shedding, finding that the 20% of children and adults who shed most were responsible for a very high proportion of overall shedding:

- The 20% most infectious adults with influenza A(H3N2) were responsible for 78% of all shedding; and 82% in the case of influenza A(H1N1).
- The 20% most infectious children with influenza A(H3N2) were responsible for 89% of all shedding; and 96% in the case of influenza A(H1N1).

**Quality and Generalisability of the Evidence**

The quality of these studies was generally moderate to high, with a variety of study designs (one cohort, one case-control and four cross-sectional). Most studies either focused on all influenza sub-types, or reported specifically on influenza A(H1N1)pdm09 (Killingley et al., 2016; Thai et al., 2014), so we have relatively little information on the shedding patterns of seasonal influenza by sub-type.

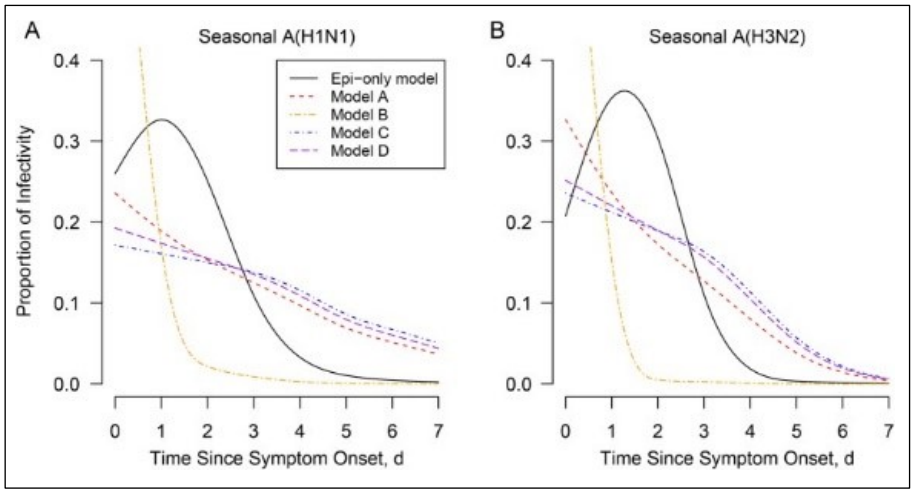
## Duration of Infectiousness

The duration of infectiousness, also referred to as the infectious period or infective period (Saito et al., 2021), is the time during which an infected person is capable of passing on infection to others.

Saito et al. (2021), who conducted a study in Japan from 2010 to 2016, calculated the mean infective period for influenza A as **1.76 days** (95% CI 0.33-4.62 days) and for influenza B as **2.62 days** (95% CI 0.54-5.75 days).

In Figure 4 below, the black line shows the proportion of infectivity that occurs each day after onset of symptoms based on epidemiological data from a 2008-2012 study of influenza transmission in Hong Kong (Tsang et al., 2015), which indicates that most infectivity occurs in the first four days after symptom onset, for influenza A(H1N1) and A(H3N2). The other lines on this graph represent attempts by the study authors to model infectivity based on viral load (shedding) or functions of viral load, with the aim of exploring whether shedding could be used as a proxy for the infectious period. However, the authors found that these models based on shedding all overestimated the proportion of transmission which took place more than 3 days after symptom onset, suggesting that the duration of shedding is typically longer than the infectious period for influenza (Tsang et al., 2015).

**Figure 4. Infectivity of Influenza, by Number of Days After Symptom Onset (Tsang et al., 2015)**




**Quality and Generalisability of the Evidence**

The evidence in this section is limited to two cross-sectional studies, albeit both of moderate to good quality. This limits the reliance that should be placed on these findings overall, and particularly in respect of different geographical contexts and influenza sub-types. The findings from Tsang et al. (2015) may be helpful in contextualising the findings of studies on influenza viral shedding (see section above) as it suggests that there is a meaningful distinction between the period of shedding and the infectious period, at least for influenza A.

## Doubling Time

Doubling time is "the average time taken for a population to double in numbers" (Porta, 2014) – in this case, the population of people infected with influenza in a given outbreak.

Gurav et al. (2017) analysed two outbreaks of influenza A(H1N1)pdm09 in Janata Vahasat slum, Pune (India) in the summers of 2012 and 2015, based on community surveillance. In 2012, they estimated the doubling time of the epidemic as 2.88 days, while in 2015 it was estimated to be 2.44 days.

Mimura et al. (2015) calculate the growth rate of influenza A(H3N2) in Japan during the 2011-12 season (0.179) and the 2012-13 season (0.106), which allows calculation of an approximate doubling time of 3.9 days in 2011-12, and 6.6 days in 2012-13.

**Quality and Generalisability of the Evidence**

Given the small number of studies, and the different sub-types of influenza studied in each, it is not possible to synthesise the results to obtain a richer picture of the doubling time of influenza. However, both studies were of moderate quality and give some useful initial indications as to the doubling time and growth rate of influenza.

## Mode of Transmission

Four modes or mechanisms of respiratory virus transmission can be defined: direct contact; indirect contact (fomite); (large) droplets; (fine) aerosols (Leung, 2021).

We found four studies exploring the mode of transmission of influenza (Table 15), and one relevant modelling study (discussed separately below).

**Table 15. Mode(s) of Transmission of Influenza**

| Study | Dates | Location | Setting | Mode | How was it measured? | Findings |
|---|---|---|---|---|---|---|
| **Fong et al. (2020)** | 2017-2018 | Hong Kong | Kindergartens and primary schools | Fomite | Swab samples collected from commonly touched surfaces | Influenza RNA found in <1% of samples (12 of 1,352). Most common on communal items such as books and doorknobs. |
| **Ikonen et al. (2018)** | 2015-16 | Finland | Airport (passenger areas) | Fomite | Swab samples collected from commonly touched surfaces | **Influenza A** found in 1 of 90 samples (1.1%). |
| | | | | Airborne | Air samples collected using Impactor FH5 sampler in passenger security check area | No influenza detected in any of the four air samples. |
| **Killingley et al. (2016)** | 2009-2011 | England | Hospital and community settings | Fomite | 671 swabs were collected from 39 surfaces touched by people infected with **Influenza A(H1N1)pdm09** | 4.9% of samples were +ve for influenza (n=33) and 0.3% yielded viable virus (n=2) |
| | | | | Airborne | Room air was sampled in the vicinity of 12 people infected with **Influenza A(H1N1)pdm09**. | 42% (n=5) air samples were PCR positive. Virus was detected in all particle sizes collected. |
| **Zhao et al. (2019)** | 2018 (Jan and Apr) | Qinhuangdao, China | Hospital | Airborne | Air was sampled daily from the outpatient hall, clinical lab, fever clinic, and children's and adults' wards over 7 days in January and 7 days in April. Outdoor samples were taken as controls. | **Influenza A and B** were only detected in January, and only in in-patient areas: on 1/7 days in the fever clinic; 2/7 days in the children's wards; 1/7 days in the adult ward. |

The studies found very limited evidence of influenza transmission by fomites. Some evidence of transmission via airborne routes was found by Killingley et al. (2016) and Zhao et al. (2019). Killingley et al. (2016) tested samples for evidence of viable virus, and found this in only 0.3% of surface samples.

In addition to the studies tabulated above, we note the findings of a modelling study by Xiao et al. (2018). This study did not directly measure the transmission of influenza, but took data from a 2008 outbreak of influenza in a Hong Kong hospital in 2008, and fitted models of different transmission routes to the actual patterns of influenza spread within the ward. They found that spread was best explained by a two-route transmission, with airborne transmission contributing to 94% of spread and fomite transmission 6%.

### Quality and Generalisability of the Evidence

Overall, the quality of studies on the mode of transmission of influenza was poor. Key limitations include the small sample sizes; lack of testing for the viability of virus detected in aerosols and fomites (with the exception of Killingley et al. (2016)); and no exploration of whether the virus detected in fomites or aerosols actually contributed to onward transmission of influenza.

## DISCUSSION

The principal aim of this review was to update the planning assumptions underpinning the World Health Organization (2017) Pandemic Influenza Risk Management Guide (PIRM). The primary focus of this Discussion is to examine how the findings of this review correspond with those assumptions, set out in Appendix 2 (A2.1 and A2.2) to the PIRM.

**Mode of transmission:** The PIRM states that "droplet and contact transmission appear to be major routes of transmission for seasonal influenza" (World Health Organization, 2017). This review found

little new evidence to support the transmission of influenza by fomites, but two studies (Killingley et al., 2016; Zhao et al., 2019) appear to provide further evidence in support of airborne transmission. A modelling study by Xiao et al. (2018) likewise suggests that airborne transmission would explain around 94% of the spread of influenza in a given outbreak, with fomite transmission responsible for the remaining 6%. These findings indicate that the existing planning assumptions remain valid.

**Incubation period:** The PIRM assumes an incubation period of 1-3 days for pandemic influenza (World Health Organization, 2017). Studies of influenza A or B found a mean duration of between 1.4 to 1.66 days (Liu et al., 2021; Saito et al., 2021).

Studies focusing specifically on avian influenza A(H7N9) found longer incubation periods, of 3.4-4 days (Virlogeux et al., 2015; Zhou et al., 2019). A similar trend of longer incubation periods for avian influenza A(H5N1) was reported in the PIRM (World Health Organization, 2017).

These findings suggest that the planning assumptions remain valid. However, if a future pandemic has its source in zoonotic transmission, the possibility of longer incubation periods should be borne in mind and researched accordingly.

**Latent period:** The PIRM assumes a latent period of 0.5-2 days for pandemic influenza (World Health Organization, 2017). We found no studies to update these assumptions.

**Shedding and Duration of infectiousness:** The PIRM assumes a duration of infectiousness of "about 5 days in adults and possibly longer in children."

Tsang et al. (2015) report modelling work which would support a clear distinction between *duration of viral shedding* and *duration of infectiousness (or infective period)* for influenza, with the latter period notably shorter than the former. We found only one study focused directly on the infective period (Saito et al., 2021), which calculated the mean infective period for influenza A as 1.76 days (95% CI 0.33-4.62 days) and for influenza B as 2.62 days (95% CI 0.54-5.75 days).

Four studies explored viral shedding duration, finding a range from 4.6 to 7 days. Studies consistently found higher rates and duration of shedding in children (especially very young children) compared to adults, which supports the existing planning assumptions. Notably, Ng et al. (2016) and Thai et al. (2014) also found some evidence of presymptomatic shedding, particularly among children.

We would suggest that, while there is not currently enough evidence to revise the assumptions in PIRM, based on Saito et al. (2021) and Tsang et al. (2015) it is possible that the infective period for adults may be overstated. **More research on the infective period of influenza (as distinct from the duration of viral shedding) is needed to support this.**

**Basic reproduction number:** The PIRM assumes a basic reproduction number ($R_0$) for pandemic influenza of 1.1 to 2.0 days. We found a range of $R_0$ values for influenza A(H1N1) from 0.92 (95% CI 0.71-1.51) to 1.82 (95% CI not given). This suggests the planning assumptions remain generally valid.

However, we found no studies on $R_0$ for influenza A(H3N2) or influenza B. This is an important gap in terms of planning assumptions for seasonal influenza.

Additionally, we found two studies on human-to-human transmission of avian influenza A(H7N9), both of which estimated much lower R0 of 0.08 - 0.27. This suggests that, in the case of future human-to-human transmission of zoonotic strains of influenza, it may be important to measure the reproduction number directly, rather than relying on planning assumptions for current human strains of influenza.

**Generation time / serial interval:** Studies of influenza A and B reported a range of mean serial intervals from 2.0 to 5.9 days. Two studies of human-to-human transmission of avian influenza A(H7N9) found much longer serial intervals, of around 9 days (Yang et al., 2015; Zhou et al., 2019). While the PIRM does not currently state assumptions about the serial interval of influenza, an accurate measure of the serial interval is important in modelling R0. It may therefore be helpful to put forward an evidence-based planning assumption in future updates of the PIRM.

**Doubling time:** Only two studies reported the doubling time or growth rate of influenza, which varied from 2.44 to 2.88 days for influenza A(H1N1)pdm09 (Gurav et al., 2017) and 3.9 to 6.6 days for influenza A(H3N2) (Mimura et al., 2015). No assumptions on doubling time are included in the PIRM at present, and it is not possible to provide a robust assumption on the basis of only two studies; however, this information may usefully contribute (along with data on $R_0$ and serial intervals) to greater understanding of the likely transmission time and dynamics of influenza.

**Attack rate:** While there are currently no assumptions of influenza attack rate stated in the PIRM, an understanding of likely attack rates in different settings may help in predicting the spread of influenza.

We found numerous studies attempting to measure the attack rate of influenza in healthcare and community settings. There was extensive variation between influenza sub-types, between years, and between different settings and geographical locations. These differences may also have been driven in part by significant differences in methodological approaches between studies (for example, Dahlgren et al. (2021) include a high proportion of asymptomatic and paucisymptomatic participants, which may well have informed their comparatively high attack rate measurements).

In view of these findings, we consider that, for the purpose of planning assumptions, it may be more important to draw attention to the extent of possible variations in attack rates (and to indicate that situation-specific measurements of attack rates will be needed) than to try and synthesise a single attack rate assumption for influenza.

**Secondary attack rate:** Given the contribution of within-household transmission to the overall spread of influenza, an understanding of secondary attack rates (especially in household settings) may also help to understand transmission dynamics.

### Gaps in the Evidence Base

The studies in this review build on, and further strengthen, the evidence base used to guide planning assumptions in the PIRM (World Health Organization, 2017).

We identified three notable gaps in the evidence base: in respect of **mode of transmission**, **duration of infectiousness** and **attack rate**.

In terms of mode of transmission, while a number of studies investigated fomite and airborne transmission, study quality was generally moderate to poor. Studies generally did not explore the viability of virus particles transmitted via different routes. Although airborne transmission is assumed to be the dominant route of influenza spread, few studies explored the dynamics of airborne transmission in different settings, which would be useful in informing infection prevention and control measures.

In terms of duration of infectiousness, no studies were found on the latent period of influenza, and only one directly on the infective period (Saito et al., 2021). Several studies of viral shedding were found, and more work is needed to determine the extent to which viral shedding can be used as a

proxy for the infective period (Tsang et al., 2015); to examine the contribution of presymptomatic shedding to influenza transmission; and to help develop separate planning assumptions, if needed, for the duration of infectiousness in children as compared to adults.

In terms of attack rate, we found considerable variation between influenza sub-types and in different settings and time periods. At present we can only draw attention to the significant variation that exists. More studies of the same influenza sub-types, in similar settings and time periods, might help to consolidate the evidence base and establish whether clear patterns exist, in terms of the attack rates of particular sub-types or in particular settings.

Finally, in most studies, the presence of influenza was confirmed by PCR testing only, and viral culture was seldom used.

### Zoonotic Influenza

This review included a small number of studies of human-to-human transmission of avian influenza A(H7N9). The planning assumptions in the current PIRM include some notes about human-to-human transmission of avian influenza A(H5N1) (World Health Organization, 2017).

While the numbers of studies included are too small to determine whether this is a significant difference, we note that, in both cases, there appear to be substantial differences in key transmission parameters between these two influenza strains of zoonotic origin, and established human influenza strains. Notably, the incubation periods of both appear to be longer, which has implications for observation and quarantine measures, if required.

If a future influenza outbreak begins with zoonotic spillover, it may be useful for planners to be aware of this trend, and to understand the importance of researching and measuring the parameters of the new disease strain in real time; rather than relying too heavily on planning assumptions for existing human strains of influenza, which may not provide an accurate picture of how zoonotic strains will behave.

### Strengths and Limitations of the Review

This rapid review was conducted using adapted systematic review methodology. Constraints of this approach include limiting our search to three databases (although the databases most relevant to the review question were selected); excluding studies in languages other than English; conducting data extraction and quality appraisal by one reviewer per study; and restricting our scope to ten parameters of interest.

However, this approach enabled us to conduct a thorough review within a reasonable timeframe, in order to provide a summary of the best-available evidence, which may be used to inform the assumptions underpinning future planning for the management of influenza outbreaks. It avoids duplication of effort by updating the existing evidence base, starting from 2013 when the last searches for the current PIRM were carried out.

This review builds on and updates the influenza planning assumptions in the PIRM (World Health Organization, 2017). As such, it focuses on transmission parameters which are directly useful to planners, in order to provide evidence which may be relevant to real-world decision-making in respect of pandemic and seasonal influenza.

### Implications for Research, Policy and Practice

This review aimed to synthesise the best available evidence on core epidemiological parameters in respect of influenza. As such, it provides some core estimates of these parameters which may be used to inform the assumptions underpinning planning and guidelines for the management of future influenza outbreaks, best practices for infection control, and so on.

It has also identified several limitations in the current evidence base, particularly in respect of mode of transmission, duration of infectiousness and influenza attack rates; which would benefit from further high-quality studies in order to strengthen our understanding.

**CONCLUSIONS**

In this review we have synthesised the latest evidence on 9 out of 10 key transmission parameters for influenza (no further studies on the latent period of influenza were found). These findings continue to support the planning assumptions which form the basis of the World Health Organization (2017) Pandemic Influenza Risk Management guidelines. They also identify a number of areas (particularly related to mode of transmission, attack rates, and duration of infectiousness) where further research could strengthen those assumptions; and suggest that there may be meaningful differences between the behaviour of zoonotic influenza strains which begin human-to-human transmission, versus that of strains already endemic in humans, which might need to be taken into consideration in future planning guidelines.

# APPENDICES

## Appendix 1: Review Protocol

### 1. Review title

***What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of seasonal and pandemic influenza?***

### 2. Search strategy

We will conduct searches in: Medline, Embase, and Global Health (CABI).
Preliminary search strategy in Medline:

| | |
|---|---|
| 1 | exp Disease Transmission, Infectious/ |
| 2 | transmission.fs. |
| 3 | infections/ or exp cross infection/ |
| 4 | (transmission* or serial interval or reproducti* number or reproducti* ratio).ti,ab. |
| 5 | 1 or 2 or 3 or 4 |
| 6 | Influenza, Human/ |
| 7 | exp influenzavirus a/ or exp influenzavirus b/ |
| 8 | (influenza* or flu).ti,ab. |
| 9 | 6 or 7 or 8 |
| 10 | 5 and 9 |
| 11 | epidemiologic studies/ or exp cohort studies/ |
| 12 | clinical trial/ or controlled clinical trial/ or randomized controlled trial/ |
| 13 | ep.fs. |
| 14 | (epidemiolog* or clinical trial or controlled trial).ti,ab. |
| 15 | 11 or 12 or 13 or 14 |
| 16 | ((avian or swine or veterinary).ti,ab. or animals/) not humans/ |
| 17 | 10 and 15 |
| 18 | 17 not 16 |
| 19 | limit 18 to yr="2013 -Current" |

Prior systematic reviews will be scrutinised for relevant included studies.

### 3. Selection Criteria

| | **Include** | **Exclude** |
|---|---|---|
| **Population** | Any (human) | Animal studies |
| **Exposure** | Seasonal or pandemic influenza (lab-confirmed) | ILI or SARI<br>Any other virus / condition |
| **Comparator** | N/A | N/A |
| **Outcome** | • **Attack rate(s)**<br>• **Generation interval(s)**<br>• **Latent period & incubation period** | Symptomatology<br>Risk factors for transmission<br>% symptomatic |

| | | |
|---|---|---|
| | • **Duration of infectiousness**<br>• **Reproduction number**<br>• **Doubling time / growth rate**<br>• **Mode(s) of transmission** | Zoonotic transmission |
| **Study types** | Observational epidemiological studies<br>RCTs and quasi-experimental studies | Case series & case reports<br>Animal studies<br>In-vitro studies<br>Modelling studies<br>Papers with no data (commentaries, etc) |
| **Language** | English | Languages other than English |
| **Setting** | Any | None |
| **Geographical location** | Any | None |
| **Publication date** ~~**Timeframe**~~ | September 2013 onwards | Prior to September 2013 |

## 4. Screening

Title and abstract screening and full-text screening will be carried out in duplicate using Covidence; conflicts will be resolved by discussion between the two reviewers involved, or by a third member of the team.

## 5. Data Extraction

Data extraction will be completed by a single reviewer. A data extraction form will be drawn up in Excel and piloted by the team. We plan to extract the following data:

- Title
- Author(s)
- Study type
- Year published
- Dates of study
- Country
- Setting
- Study population size
- Relevant covariates e.g.
    - Age
    - Gender
    - Race or ethnicity
    - Vaccination status (Influenza)
    - Underlying conditions
    - Occupation
    - Socioeconomic status
    - Any coinfections
- Exposure(s)
    - Influenza virus type (A/B/...)
    - Subtype (e.g. H1N1)
- Diagnostic test(s) used
- Outcome [with confidence intervals]:

    - Attack rate(s)
    - Generation interval(s)
    - Latent period
    - Incubation period
    - Duration of infectiousness
    - Reproduction number
    - Mode(s) of transmission
- Study conclusions
- Study limitations

(Note this list may be revised subject to piloting of data extraction form)

**6. Quality Assessment**

Quality assessment will be carried out by a single reviewer, using the relevant JBI Critical Appraisal tool for each study design.

**7. Strategy for data synthesis**

We will produce a narrative synthesis of our findings. As far as possible, we will use the structure of "Annex 2: Planning Assumptions" (in particular, sections A2.1 and A2.2 on pp 47-49) in the WHO Pandemic Influenza Risk Management guidelines to inform our synthesis.

If possible, we will produce a table comparing influenza and COVID-19 transmission parameters. We will use COVID-19 data provided by the WHO or, if unavailable, sourced from one or more systematic reviews listed in the COVID-END Inventory of Best Evidence Syntheses. We will not carry out a review of original studies in respect of COVID-19.

**8. Subgroup analysis**

If possible, we will analyse our findings separately for:

- Influenza Type A and Type B
- Pandemic influenza and seasonal influenza
- Pre- and post- November 2019 (before vs during the COVID-19 pandemic)
- Different age groups
- Setting (community / hospital)

## Appendix 2: Search Strategy

Embase (Ovid) <1980 to 2022 Week 17>
Date of search: 5 May 2022
Results total: 3984

| | | |
|---|---|---|
| 1 | exp disease transmission/ | 223283 |
| 2 | (transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab. | 660729 |
| 3 | 1 or 2 | 766615 |
| 4 | influenza/ or exp influenza a/ or influenza b/ | 91135 |
| 5 | influenza virus/ or exp influenzavirus a/ or exp influenzavirus b/ | 35101 |
| 6 | (influenza* or flu).ti,ab. | 153321 |
| 7 | 4 or 5 or 6 | 179340 |
| 8 | exp epidemiology/ | 3945223 |
| 9 | cohort analysis/ | 834183 |
| 10 | clinical trial/ or exp controlled clinical trial/ or multicenter study/ or exp case control study/ | 1802511 |
| 11 | ep.fs. | 1100336 |
| 12 | (epidemiolog* or clinical trial or controlled trial).ti,ab. | 940479 |
| 13 | 8 or 9 or 10 or 11 or 12 | 6544557 |
| 14 | (exp animal/ or nonhuman/) not exp human/ | 6413269 |
| 15 | 3 and 7 and 13 | 9670 |
| 16 | 15 not 14 | 8169 |
| 17 | limit 16 to yr="2013 -Current" | 3984 |

Global Health (Ovid) 1973-2022 week 17
Date of search: 5 May 2022
Results total: 1479

| | | |
|---|---|---|
| 1 | exp disease transmission/ | 116672 |
| 2 | (transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab. | 141969 |
| 3 | 1 or 2 | 207785 |
| 4 | exp influenza/ | 32310 |
| 5 | influenza viruses/ or exp influenzavirus a/ or exp influenzavirus b/ | 31795 |
| 6 | (influenza* or flu).ti,ab. | 42806 |
| 7 | 4 or 5 or 6 | 43935 |
| 8 | epidemiology/ or cohort studies/ or clinical trials/ or randomized controlled trials/ or case-control studies/ | 401539 |
| 9 | (epidemiolog* or clinical trial or controlled trial).ti,ab. | 181514 |
| 10 | 8 or 9 | 457390 |
| 11 | exp animals/ not man/ | 416928 |
| 12 | 3 and 7 and 10 | 3007 |
| 13 | 12 not 11 | 2568 |
| 14 | limit 13 to yr="2013 -Current" | 1479 |

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to May 04, 2022>
Date of search: 5 May 2022
Results total: 2516

| | | |
|---|---|---|
| 1 | exp Disease Transmission, Infectious/ | 78381 |
| 2 | transmission.fs. | 160296 |
| 3 | (transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab. | 586573 |
| 4 | 1 or 2 or 3 | 696326 |
| 5 | Influenza, Human/ | 54748 |
| 6 | exp influenzavirus a/ or exp influenzavirus b/ | 48978 |
| 7 | (influenza* or flu).ti,ab. | 135365 |
| 8 | 5 or 6 or 7 | 143354 |
| 9 | exp epidemiologic studies/ or exp cohort studies/ | 2938449 |
| 10 | clinical trial/ or controlled clinical trial/ or randomized controlled trial/ | 909287 |
| 11 | ep.fs. | 1962622 |
| 12 | (epidemiolog* or clinical trial or controlled trial).ti,ab. | 711383 |
| 13 | 9 or 10 or 11 or 12 | 5065428 |
| 14 | ((avian or swine or veterinary).ti,ab. or animals/) not humans/ | 4986300 |
| 15 | 4 and 8 and 13 | 7015 |
| 16 | 15 not 14 | 5963 |
| 17 | limit 16 to yr="2013 -Current" | 2716 |

## Appendix 3: All Included Studies – Quality Appraisal and Transmission Parameters

Table A3.1 below lists all studies included in this review, together with the JBI checklist used for quality appraisal, and the outcome of the quality assessment. The right-hand columns show which transmission parameter(s) each study relates to.

**Table A3.1. List of all included studies, with quality appraisal and transmission parameters**

| Study | Best fit for QA | Quality | Attack rate | SAR | R0 | Generation time | Incubation period | Shedding | Infectiousness | Doubling time | Mode of transmission | Latent period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Von-Mollendorf-2018 | Case-control | High | | | | | | Yes | | | | |
| Cohen-2021 | Cohort | High | Yes | Yes | | Yes | | Yes | | | | |
| Dahlgren-2021 | Cohort | High | Yes | Yes | | | | | | | | |
| Tam-2018 | Cohort | Moderate | Yes | | | | | | | | | |
| Wei-2018 | Cohort | High | Yes | | | | | | | | | |
| Whelan-2016 | Cohort | Low | Yes | | | | | | | | | |
| Chan-2013 | Cross-sectional | Low | Yes | | | | | | | | | |
| Dennis-2020 | Cross-sectional | Moderate | Yes | | | | | | | | | |
| Eibach-2014 | Cross-sectional | Low | Yes | | | | | | | | | |
| Fong-2020 | Cross-sectional | Moderate | | | | | | | | | Yes | |
| Hooshmand-2021 | Cross-sectional | Moderate | Yes | | | | | | | | | |
| Ikonen-2018 | Cross-sectional | Low | | | | | | | | | Yes | |
| Ip-2017 | Cross-sectional | Low-Moderate | | Yes | | | | Yes | | | | |
| Iyengar-2015 | Cross-sectional | High | | Yes | | Yes | | | | | | |
| Kamigaki-2014 | Cross-sectional | Low | Yes | | | | | | | | | |
| Killingley-2016 | Cross-sectional | Moderate | | | | | | Yes | | | Yes | |
| Lau-2013 | Cross-sectional | High | | | | | | Yes | | | | |
| Levy-2013 | Cross-sectional | High | | Yes | | Yes | | | | | | |
| Liu-2021 | Cross-sectional | Low | | | | | Yes | | | | | |
| Mimura-2015 | Cross-sectional | Moderate | | | | | | | | Yes | | |
| Ng-2016 | Cross-sectional | High | | | | | | Yes | | | | |
| Parkash-2019 | Cross-sectional | High | Yes | | | | | | | | | |
| Petrie-2013 | Cross-sectional | High | | Yes | | Yes | | | | | | |
| Saito-2021 | Cross-sectional | Moderate | | Yes | | | Yes | | Yes | | | |
| Sansone-2019 | Cross-sectional | Low | Yes | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tamo-2022 | Cross-sectional | High | | Yes | | | | | | | | |
| te Beest-2013 | Cross-sectional | High | | | | Yes | | | | | | |
| Thai-2014 | Cross-sectional | High | | Yes | | Yes | | Yes | | | | |
| Tsang-2015 | Cross-sectional | High | | Yes | | | | | Yes | | | |
| Vera-2014 | Cross-sectional | Moderate | Yes | | | | | | | | | |
| Virlogeux-2015 | Cross-sectional | Moderate | | | | | Yes | | | | | |
| Yang-2015 | Cross-sectional | Low-Moderate | | Yes | Yes | Yes | | | | | | |
| Zhao-2019 | Cross-sectional | Low | | | | | | | | | Yes | |
| Zhou-2019 | Cross-sectional | Low | | | | Yes | Yes | | | | | |
| Gurav-2017 | Prevalence | Moderate | Yes | | Yes | | | | | Yes | | |
| Inglis-2013 | Prevalence | High | Yes | | Yes | | | | | | | |
| Rao-2019 | Prevalence | Low | Yes | | | | | | | | | |
| Chong-2016 | Modelling | * | | | Yes | | | | | | | |
| Liu-2015 | Modelling | * | | | Yes | | | | | | | |
| White-2014 | Modelling | * | | | Yes | | | | | | | |
| Xiao-2018 | Modelling | * | | | | | | | | | Yes | |
| Yang-2013 | Modelling | * | | | Yes | | | | | | | |
| Davila-Torres-2015 | Modelling [for R0] | * | | | Yes | | | | | | | |
| Pamaran-2013 | Modelling [for R0] | * | | | Yes | | | | | | | |

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