UK Health Security Agency

Incubation and infectious period of influenza A (H1N1v and H1N2v)

A rapid evidence summary

Contents

Main messages

1. This rapid evidence summary (search up to 27 November 2023) identified and summarised evidence relating to the incubation period (the time between contracting an infection and symptom onset) and infectious period (the timeframe in which an individual may transmit the infection to others) of influenza A H1N1 variant (H1N1v) and H1N2 variant (H1N2v). There were 5 included studies (1 to 5).

2. Published evidence was only available for the incubation or infectious period of H1N1v and includes both children and adults. There were no studies identified for H1N2v. Included evidence was restricted to studies published in English language using the terms ‘H1N1v’, ‘H1N1 variant’, ‘H1N2v’, or ‘H1N2 variant’ or variations of these.

3. One study investigated the incubation period of H1N1v in 335 laboratory confirmed cases from England's Health Protection Agency (HPA) national influenza database (FluZone). The exact exposure and onset of symptoms was known for 72 cases in whom the incubation period was reported to be 2.5 days (SD: 2.1 days).

4. No studies reported direct measures of the infectious period of H1N1v, however, 4 studies reported indirect measures including; serial interval (the time between symptom onset in the index case and symptom onset in a secondary case) (2 to 4) and viral load (the amount of detectable virus) in nasopharyngeal (nose and throat) swabs over time (1).

5. Mean serial interval of H1N1v ranged from 2.5 to 3.1 days across 2 studies (2, 3). In the third study median serial interval was reported to be 3 days (4).

6. In one study of 60 H1N1v cases, people tested on day one post symptom onset had a higher viral load than those tested on other days, up to day 3 post symptom onset. However the study did not assess the change in viral load in an individual over time so caution should be applied in the interpretation of these results (1).

7. The findings of this evidence summary are based on a limited number of observational studies, most of which only included a small number of cases. Most studies relied on historical data collected at the time of the case being identified. Risk of bias in each study was not assessed, however the general limitations described in the report, the small number of studies found for H1N1v and lack of evidence for H1N2v means there is insufficient evidence to draw firm conclusions on the incubation or infectious periods of H1N1v or H1N2v.

Purpose

The purpose of this rapid evidence summary was to identify and summarise the available evidence on the incubation and infectious period of influenza A H1N1 variant (H1N1v) and H1N2 variant (H1N2v).

Methods

The review question was:

1. What are the incubation and infectious periods of influenza A H1N1v and H1N2v in humans?

The incubation period was defined as the time between infection and the onset of symptoms. The infectious period was defined as the time period during which an individual may infect others. The infectious period is difficult to measure directly, therefore indirect measures of infectious period were also considered relevant to inform this part of the question, such as:

- culture positivity over time
- serial interval (the time between symptom onset in an initial case and symptom onset in those the infection is passed to)
- generation time (the time between infection in an initial case and infection in those the infection is passed to)
- time to peak viral load (time taken to highest amount of detectable virus)
- viral load over time (amount of detectable virus over time)

The databases Ovid Medline and Embase, Latin American and Caribbean Health Sciences Literature (LILACs) and Web of Science Preprint Citation Index were searched for studies published up to 27 November 2023.

A protocol was produced before the literature search was conducted, including the review question above, the eligibility criteria, and full details of all other methods, see Annexe A.

Screening of title and abstracts was undertaken in duplicate by 2 reviewers for 10% of studies, with the remainder completed by one reviewer. Screening of full text was undertaken by one reviewer and checked by a second. Any disagreements were resolved by discussion with a third independent reviewer. For a full list of papers excluded during full text screening with reasons for exclusion, see Annexe B.

There was one protocol clarification. Studies were only included if they specified that they measured outcomes for influenza A H1N1v, H1N1 variant, H1N2v, or H1N2 variant rather than

just H1N1 for example. This was to ensure that evidence for this review was relevant to the recently identified strain in the United Kingdom (influenza A H1N2v) (6).

Evidence

In total, 3,677 studies were screened on title and abstract, of which 16 studies were screened on full text, and 5 were included in this evidence summary (1 to 5). An additional 6 studies were identified from papers that were screened at full text, however none of these met the inclusion criteria. A full overview of the study selection process is presented in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram in Annexe C (Figure C1).

The 5 included studies were carried out in Australia (3), Hong Kong (1), Japan (4), the Netherlands (2), and the United Kingdom (5). All studies included both adults and children, ranging from people aged from 5 months to 85 years. Although there was no date restriction on the search, all identified evidence was from 2009. The study periods ranged from April to July 2009 (1 to 5). Four of the studies were retrospective cohorts (1 to 3, 5), and one was a prospective cohort (4). Study characteristics and results are presented in Table D1.

Incubation period

Tom and others studied the incubation period of H1N1v in 335 cases with a known date of onset of symptoms and some information available on the timing of exposure, from England's Health Protection Agency (HPA) national influenza database (FluZone) between May and June 2009 (5). The authors extracted timing of exposure to H1N1v (date of first, last, or ideally both dates of exposure as well as symptom onset to ascertain exact incubation period). Average incubation period was reported as the mean and median. For the 72 cases where the exact date of exposure to H1N1v was known, the mean incubation period was 2.5 days (standard deviation [SD]: 2.1 days).

The mean incubation period across all cases including those where exposure to H1N1v fell within a known interval (not defined by the study) but the exact date was unknown, was 1.7 days (SD: 2.0 days), and the median was 1 day (95% CI: 0.8 to 1.2 days). A subgroup analysis by age group suggested the mean incubation time was shorter for those aged under 15 years (1.2 days, SD: 2.5 days, n=132) compared to those aged 15 years and over (1.9 days, SD: 2 days, n=203). However, there is uncertainty around these mean values and this analysis also included data from people in which the exact exposure was unknown.

No studies reported on the incubation period of H1N2v.

Infectious period

All available evidence was for H1N1v. Although no studies reported direct measures of the infectious period of H1N1v, 4 studies reported on indirect measures. These were 3 studies reporting on serial interval (2 to 4) and one on viral load (1).

Studies reported average serial interval as the mean or the median. Estimates of the mean serial interval of H1N1v taken from 2 studies ranged from 2.5 to 3.1 days (2, 3). Hahne and others reported a mean serial interval of 2.7 days (SD: 1.1 days) from 32 H1N1v cases and their respective index cases (the individuals who infected them), in a retrospective analysis of data obtained from Municipal Health Service records in the Netherlands (2). McBryde and others reported a mean serial interval of 2.9 days (SD: 1.4 days) amongst 750 H1N1v cases and their respective index cases, in a retrospective analysis of case data available for Victoria, Australia (3).

Odaira and others undertook prospective daily follow up of household contacts of known index H1N1v cases for approximately 8 days, in Kobe city, Japan. They reported a median serial interval time of 3 days (range from one to 5 days) amongst 14 secondary cases in household contacts of H1N1v, and their 13 respective index cases (4). Most index cases in this study (92%) received antiviral treatment, and 42% of household contacts received antiviral prophylaxis, however the study did not investigate the effect this had on serial interval time compared to those who did not receive antivirals (4).

Cheng and others measured viral load in nasopharyngeal (nose and throat) swabs from 60 H1N1v cases, categorised by the number of days between symptom onset and when the sample was taken (0, 1, 2 or 3 days) (1). The authors reported that people tested on day one post symptom onset had the highest amount of virus detectable compared to those tested on other days, up to day 4 of symptom onset. However, the viral load was higher on day 3 compared to day 2, and there was no data for viral load 4 days or more after symptom onset, so the full trend of viral load over time could not be established. In addition, only one swab was taken from each case, rather than consecutive swabs from cases over time. The estimate of viral load at each day post symptom onset is therefore an average across cases who were swabbed on that day. These results therefore do not inform change in viral load in an individual over time.

No studies reported on the infectious period of H1N2v.

Health inequalities

No studies discussed health inequalities with regards to measurement of incubation or infectious period in different vulnerable groups, therefore it was not possible to examine health inequalities in this report.

Limitations

This evidence summary was conducted at pace, following streamlined methodology. Studies were limited to those which specified the terms H1N1v, H1N1 variant, H1N2v, or H1N2 variant or variations of these in their title, abstract and keywords. This restriction in terminology was agreed to ensure included evidence was relevant to the newly identified influenza H1N2v strain in the United Kingdom (6). However, study authors may not have used this terminology consistently in the titles and abstracts of their studies. As a result, relevant studies or information in studies may have been missed.

Included studies were limited to those published in the English language, as translation resources were not available within the short timeframe of the development of this review. All potentially relevant studies were selected at title and abstract stage. Only 2 non-English language studies were identified, neither of which appeared relevant to include; one in Russian which was a review article rather than a primary study, and the second in Spanish which did not appear to have studied incubation or infectious period from details in the abstract. However it is possible that additional detail may have been available in the full text of the article.

As per the study protocol critical appraisal was not performed, in order to ensure rapid completion of this work. This limits the interpretation of the findings, although important limitations of the evidence have been highlighted in this report.

There was a very limited amount of evidence available for this review question. Most studies were retrospective and exact details of exposure were not always available. All evidence for infectious period was based on serial interval estimate, with one study also looking at viral load, but this was not assessed in individuals over time. It should also be noted that while higher viral loads may be indicative of a higher chance of being infectious, they do not necessarily indicate infectiousness. Caution in interpreting these findings is warranted, and firm conclusions cannot be drawn.

Evidence gaps

No studies reported on the incubation or infectious period of H1N2v. In addition, no studies directly reported on the infectious period of H1N1v, only evidence on indirect measures was found.

Conclusion

All available evidence was for H1N1v, with there being no available evidence for H1H2v.

One study reported on the incubation period of H1N1v (5). In this study, incubation period in cases who had an exact exposure date to H1N1v was reported as 2.5 days (SD, 2.1 days). This varied when those without a precise date of exposure were included, and appeared to be lower for people aged under 15, although this was also based on people in whom the exact date of exposure was uncertain (5).

For the infectious period, 3 studies measured the average time between symptom onset in an initial case of H1N1v and symptom onset in those the infection is passed to (serial interval) The mean timeframe ranged from 2.5 to 3.1 days in 2 studies (2, 3) and in a third study a median timeframe of 3 days was reported (4). H1N1v viral load over time was measured in a further study up to 3 days post symptom onset, suggesting it was highest in those tested one day post-symptom onset, however this study cannot inform change in viral load in an individual over time (1).

The results for time periods for infection and incubation periods reported in this rapid evidence summary are based on a very limited number of studies, most of which only had a small number of cases and had methodological limitations. All information was for H1N1v with no relevant evidenced being identified at this time for H1N2v. The limitations in methodology and amount of evidence lead to a lack in confidence in the reliability of these results and limit the extent to which they can be generalised.

The available evidence at this time cannot reliably inform the incubation or infectious period. An increase in evidence, including evidence specifically for H1N2v may warrant an update in this rapid evidence summary.

Acknowledgments

We would like to thank colleagues within the Clinical and Public Health Response division who either reviewed or input into aspects of the review, in particular Sam Collins and Ruth Milton. We would also like to thank colleagues from across UKHSA who supported with this review; David Edwards, Anissa Lakhani, and Angie Lackenby.

Disclaimer

UKHSA's rapid reviews and evidence summaries aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, and papers on preprint servers. Please note that the reviews:

- use accelerated methods and may not be representative of the whole body of evidence publicly available
- have undergone an internal independent peer review but not an external peer review
- are only valid as of the date stated on the review

In the event that this evidence summary is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

References

1. Cheng PKC and others. 'Performance of laboratory diagnostics for the detection of influenza A(H1N1)v virus as correlated with the time after symptom onset and viral load' Journal of Clinical Virology 2010: volume 47, issue 2, pages 182 to 185
2. Hahne S and others. 'Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases' Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles [European Communicable Disease Bulletin] 2009: volume 14, issue 27, page 9
3. McBryde E and others. 'Early transmission characteristics of influenza A(H1N1)v in Australia: Victorian state, 16 May to 3 June 2009' Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles [European Communicable Disease Bulletin] 2009: volume 14, issue 42, page 22
4. Odaira F and others. 'Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009' Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles [European Communicable Disease Bulletin] 2009: volume 14, issue 35, page 3
5. Tom BD and others. 'Estimating time to onset of swine influenza symptoms after initial novel A(H1N1v) viral infection' Epidemiology and Infection 2011: volume 139, issue 9, pages 1,418 to 1,424
6. UKHSA detects human case of influenza A(H1N2)v [press release] 27 November 2023

Annexe A. Protocol

Review question

There is one review question:

1. What are the infectious period and incubation period of influenza A (H1 swine; both H1N1 and H1N2) in humans?

Only studies where participants in the study have the Swine H1N1 or H1N2 sub-type of influenza A will be included.

This evidence summary will summarise evidence (search up to 27 November 2023) on the incubation and infectious periods of influenza A (H1 Swine; H1N1 or H1N2).

For this review, the definitions used are:

- incubation period: The time between contracting an infection and symptom onset
- infectious period: The timeframe when an individual may transmit the infection to others

Inclusion and exclusion criteria are shown in Table A.1.

Table A.1. Inclusion and exclusion criteria

	Included	Excluded
Population	All humans	All animals, non-humans
Settings	All settings	
Context	Any	
Intervention or exposure	Laboratory-confirmed Influenza A (H1 Swine; H1N1 or H1N2)	Other influenza Other infectious diseases
Outcomes	Any measure of incubation period of influenza A (H1 Swine; H1N1 or H1N2) Any measure of infectious period of influenza A (H1 Swine; H1N1 or H1N2): • transmission period • culture positivity over time • serial interval and generation time • time to peak viral load • time to viral clearance • viral load over time	
Language	English	
Date of publication	Up to 27 November 2023	
Study design	Interventional trials, including: • randomised controlled trials • non-randomised controlled trials • one-arm trials • quasi-experimental studies Observational studies: • cohort studies • case-control studies • cross-sectional studies	• systematic or narrative reviews • cross-over trials • case reports (of single cases) • guidelines • opinion pieces • modelling studies • laboratory studies • ecological studies
Publication type	Published and preprint Conference abstracts	

Identification of studies

We will search Ovid Medline and Embase, Latin American and Caribbean Health Sciences Literature (LILACs) and Web of Science Preprint Citation Index for studies published up to 27 November 2023.

Screening

Screening on title and abstract will be undertaken in duplicate by 2 reviewers for at least 10% of the eligible studies, with the remainder completed by one reviewer. Disagreement will be resolved by discussion with a third reviewer.

Screening on full text will be undertaken by one reviewer and checked by a second.

Data extraction

Summary information for each study will be extracted and reported in tabular form. Information will include country, setting, study design, objective, outcomes measures, participants, study period, results and any relevant contextual data (such as timing or level of community transmission at the time of the study). This will be undertaken by one reviewer and checked by a second.

Risk of bias assessment

Risk of bias of included studies will not be assessed in this rapid evidence summary due to time constraints.

Synthesis

A narrative synthesis will be written to describe the results from this review.

Variations across populations and subgroups, for example cultural variations or differences between ethnic or social groups will be considered, where evidence is available.

Search strategy

Database: Ovid MEDLINE(R) ALL <1946 to November 27, 2023>

1. Influenza A Virus, H1N1 Subtype/ (17703)
2. Influenza A Virus, H1N2 Subtype/ (204)
3. H1N1.tw,kf. (20081)

4. H1N2.tw,kf. (453)
5. (flu adj5 (swine* or pig*)).tw,kf. (1133)
6. (influenza* adj5 (swine* or pig*)).tw,kf. (3641)
7. (H1 adj3 (pig* or swine*)).tw,kf. (166)
8. exp Swine/ and Influenza, Human/ (1046)
9. or/1-8 (26264)
10. ((Transmis* or transmit*) adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (14690)
11. (Infectious* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (6121)
12. (Contagio* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (332)
13. (Isolation adj3 (duration* or time or length* or period*)).tw,kw,kf. (3819)
14. (shed* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (3674)
15. (case* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (87720)
16. (Isolation* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (7055)
17. Virus Shedding/ (4222)
18. (PCR positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (476)
19. (Viral proliferat* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (6)
20. cycl* threshold*.tw,kw,kf. (2789)
21. CT value*.tw,kw,kf. (5278)
22. (peak* adj1 (vir* load* or vir* concentrat*)).tw,kw,kf. (414)
23. (Viral Load/ or exp Disease Transmission, Infectious/) and exp Time/ (9442)
24. serial interval*.tw,kf. (441)
25. chain of transmission.tw,kf. (401)
26. (clearance* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (8105)
27. (viral load* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (2186)
28. (virus load* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (113)
29. (virus adj2 amount* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (47)
30. (virus adj2 level* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (94)
31. incubat*.tw,kf. (345787)
32. Infectious Disease Incubation Period/ (405)
33. Time Factors/ (1230923)
34. (latent or latency).tw,kf. (193506)
35. Latent Infection/ (199)
36. (time adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (65116)
37. (period adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (16690)
38. (asymptom* adj5 (duration or period or length*)).tw,kf. (2169)
39. (generation adj3 time).tw,kf. (5758)
40. or/10-39 (1929920)
41. 9 and 40 (2124)

Database: Embase <1974 to 2023 November 27>

1. exp "influenza A (H1N1)"/ (13612)
2. "influenza a virus (h1n2)"/ (353)

3. H1N1.tw,kf. (25761)
4. H1N2.tw,kf. (478)
5. (H1 adj3 (pig* or swine*)).tw,kf. (203)
6. (flu adj5 (swine* or pig*)).tw,kf. (1589)
7. (influenza* adj5 (swine* or pig*)).tw,kf. (3982)
8. swine influenza/ (1378)
9. or/1-8 (33490)
10. ((Transmis* or transmit*) adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (16287)
11. (Infectious* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (7858)
12. (Contagio* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (334)
13. (Isolation adj3 (duration* or time or length* or period*)).tw,kw,kf. (4793)
14. (shed* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (4155)
15. (case* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (136330)
16. (Isolation* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (8875)
17. virus shedding/ (10538)
18. (PCR positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (626)
19. (Viral proliferat* adj5 (duration* or time* or length* or period* or peak*)).tw,kw,kf. (7)
20. cycl* threshold*.tw,kw,kf. (3617)
21. CT value*.tw,kw,kf. (8381)
22. (peak* adj1 (vir* load* or vir* concentrat*)).tw,kw,kf. (651)
23. (exp virus load/ or exp *disease transmission/) and time/ (682)
24. serial interval/ (145)
25. serial interval*.tw,kf. (490)
26. chain of transmission.tw,kf. (492)
27. (clearance* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (11300)
28. (viral load* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (3510)
29. (virus load* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (143)
30. (virus adj2 amount* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (55)
31. (virus adj2 level* adj5 (duration* or time* or length* or period*)).tw,kw,kf. (108)
32. incubat*.tw,kf. (424582)
33. incubation time/ (58850)
34. time factor/ (47065)
35. (latent or latency).tw,kf. (240604)
36. latent period/ or latent virus infection/ (58338)
37. (time adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (105385)
38. (period adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (24820)
39. (asymptom* adj5 (duration or period or length*)).tw,kf. (3109)
40. (generation adj3 time).tw,kf. (6243)
41. or/10-40 (1068859)
42. 9 and 41 (2171)

Web of Science Preprint Citation Index (1990 – current)

TS=(H1N1) OR TS=(H1N2) OR TS=((flu NEAR/4 (swine* or pig*))) OR TS=((influenza* NEAR/4 (swine* or pig*))) OR TS=((H1 NEAR/2 (pig* or swine*)))

And

TS=((Transmis* or transmit*) NEAR/4 (duration* or time* or length* or period* or peak*)) OR TS=((Infectious* NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=(Contagio* NEAR/4 (duration* or time* or length* or period* OR peak*)) OR TS=((Isolation NEAR/2 (duration* or time or length* or period*))) OR TS=((shed* NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=((case* NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=((Isolation* NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=(("PCR positiv*" NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=(("Viral proliferat*" NEAR/4 (duration* or time* or length* or period* or peak*))) OR TS=("cycl* threshold*") OR TS=("CT value*") OR TS=((peak* NEAR/0 ("vir* load*" or "vir* concent*"))) OR TS=("serial interval*") OR TS=("chain of transmission") OR TS=((clearance* NEAR/4 (duration* or time* or length* or period*))) OR TS=(("viral load*" NEAR/4 (duration* or time* or length* or period*))) OR TS=(("virus load*" NEAR/4 (duration* or time* or length* or period*))) OR TS=((virus NEAR/1 amount* NEAR/4 (duration* or time* or length* or period*))) OR TS=((virus NEAR/1 level* NEAR/4 (duration* or time* or length* or period*))) OR TS=(incubat*) OR TS=((latent or latency)) OR TS=((time NEAR/4 (asymptom* or symptom* or onset or "clinical presentation"))) OR TS=((period NEAR/4 (asymptom* or symptom* or onset or "clinical presentation"))) OR TS=((asymptom* NEAR/4 (duration or period or length*))) OR TS=((generation NEAR/2 time))

25 results.

LILACs (Latin American and Caribbean Health Sciences Literature)

"swine flu" OR "swine influenza" OR "H1N1" or "H1N2"

468 results.

Annexe B. List of excluded studies

Wrong outcome (n=12)

Baldanti and others. 'Severe outcome of influenza A/H1N1/09v infection associated with 222G/N polymorphisms in the haemagglutinin: a multicentre study' Clinical Microbiological Infections 2011: volume 17, issue 8, pages 1,166 to 1,169

Chen X and others. 'Global epidemiology of human infections with variant influenza viruses, 1959 to 2021: a descriptive study' Clinical Infectious Diseases 2022: volume 75, issue 8, pages 1315 to 1323

Health Protection Agency West Midlands H1N1v Investigation Team. 'Preliminary descriptive epidemiology of a large school outbreak of influenza A(H1N1)v in the West Midlands, United Kingdom, May 2009' Eurosurveillance 2009: volume 14, issue 27, page 19,264

Jesan T and others. 'Epidemiological dynamics of the 2009 Influenza A(H1N1)v outbreak in India' Arxiv 2010

Kar-Purkayastha and others. 'The importance of school and social activities in the transmission of influenza A(H1N1)v: England, April to June 2009' Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles [European Communicable Disease Bulletin] 2009: volume 14, issue 33, page 20

Maravi-Poma E and others. 'Severity of 2009 pandemic influenza a (H1N1)v infection in pregnant and non-pregnant women in Spain' Intensive Care Medicine 2010: volume 2, page S368

Martin-Loeches I and others. 'Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients' Critical Care 2011: volume 15, issue 6, page R286

Rello J and others. 'Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain' Critical Care 2009 volume 13, issue 5, page R148

Rodriguez A and others. 'Critically ill patients with 2009 influenza a (H1N1)v in Spain' Intensive Care Medicine 2010: volume 2, page S318

Sansonetti P and others. 'Immune response to influenza A(H1N1)v in HIV-infected patients' Journal of Infection in Developing Countries 2014: volume 8, issue 1, pages 101 to 109

Schnepf N and others. 'High burden of non-influenza viruses in influenza-like illness in the early weeks of H1N1v epidemic in France' PLoS ONE 2011: volume 6, issue 8, page e23514

van Hoek AJ and others. 'The impact of pandemic influenza H1N1 on health-related quality of life: a prospective population-based study' PLoS ONE: volume 6, issue 3, page e17030

Wrong language (n=2)

Fisun A and others. '[Swine flu: epidemiology, diagnostics, treatment, and prophylaxis]' Voenno-Meditsinskii Zhurnal 2009: volume 330, issue 7, pages 46 to 54

Miranda-Choque E and others. 'Niños hospitalizados con neumonía por influenza AH1N11/2009 pandémico en un hospital de referencia de Perú' Revista Peruana de Medicina Experimental y Salud Publica 2011: volume 28, pages 610 to 616

Wrong study type (n=1)

Hens N and others. 'Robust reconstruction and analysis of outbreak data: influenza A(H1N1)v transmission in a school-based population' American Journal of Epidemiology 2012: volume 176, issue 3, pages 196 to 203

No full text available (n=2)

Diaz, E and others. 'Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza' Journal of Infection 2012: volume 64, issue 3, pages 311 to 318

Maraví-Poma E and others. 'Severe 2009 A/H1N1v influenza in pregnant women in Spain' Critical Care Medicine 2011: volume 39, issue 5, pages 945 to 951

Annexe C. PRISMA flow diagram

Figure C1. Study selection process

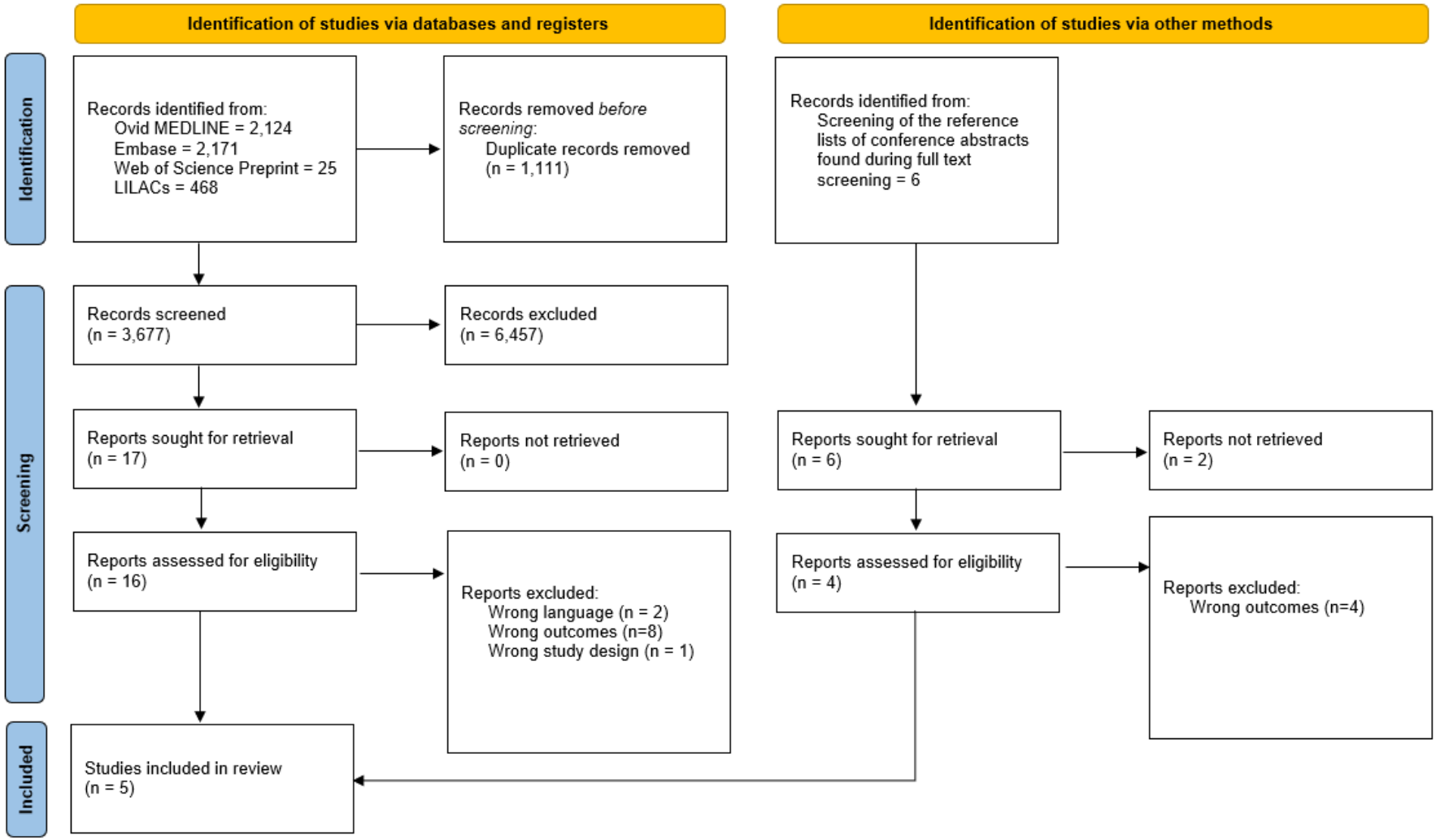

Figure C1. PRISMA diagram – alt text

A PRISMA diagram showing the flow of studies through this review, ultimately including 5 studies.

From identification of studies via databases and registers, n=4,788 records identified from databases:

- Ovid Medline (n=2,124)
- Ovid Embase (n=2,171)
- Web of Science Preprint Citation Index (n=25)
- (n=468)

From these, 1,111 records were removed as duplicates before screening:

This left n=3,677 records screened, of which n=3,660 were excluded, leaving n=17 papers sought for retrieval. Of these, n=5 studies were included in the review.

Studies were also identified via other methods: n=6 additional studies were identified from grey literature. Of these, n=0 studies were included in the review.

Reports were excluded at full text for the following reasons:

- wrong exposure (n=1)
- wrong language (n=2)
- wrong outcomes (n=12)
- wrong study design (n=1)

Leaving n=5 papers included in the review.

Annexe D. Data extraction table

Table D1. Data extraction table of included studies

CI: confidence interval, HA: hemagglutinin, RT-PCR: reverse transcriptase polymerase chain reaction, SD: standard deviation, UK: United Kingdom

Study	Country, time period	Study type (design)	Demographics (participant number, age, sex, influenza subtype)	Laboratory diagnosis method	Outcome	Outcome measurement	Findings
Cheng and others, 2010 (1)	Hong Kong, May to June 2009	Retrospective cohort	n=596 laboratory confirmed influenza A(H1N1)v cases (information on date of symptom onset available for n=587). Mean age 21 years (range: 5 months to 70 years), data on sex not reported. Of these, data available for viral load from n=60 H1N1v positive nasopharyngeal samples.	Real time RT-PCR or viral culture.	Viral load over time	Quantification of viral load in 60 H1N1v positive samples, specifically copies of HA gene of influenza A(H1N1)v virus, categorised by days after symptom onset on which the sample was taken (no serial sampling undertaken). Specific method of establishing symptom onset not specified.	Viral load peaked on day one after symptom onset (based on categorisation of samples by number of days since symptom onset, not serial sampling from the same participants) Mean HA gene copies per mL: • 0 days after symptom onset: $2.9x10^6$ (95% CI: $1.5x10^7$ to $5.8x10^5$) • 1 day after symptom onset: $8.6x10^6$ (95% CI: $2.8x10^7$ to $2.6x10^6$) • 2 days after symptom onset: $2.1x10^6$ (95% CI: $1.8x10^7$ to $2.6x10^5$) • 3 days after symptom onset: $5.3x10^6$ (95% CI: $4.0x10^7$ to $7.1x10^5$)
Hahne and others, 2009 (2)	Netherlands, April to June 2009	Retrospective cohort	n=115 laboratory confirmed influenza A(H1N1)v cases (n=108 symptomatic, n=7 asymptomatic). Age range: 0 to 69 years, data on sex not reported.	Real time RT-PCR, or viral culture, or four-fold rise in novel influenza virus A(H1N1)v specific neutralising antibodies.	Serial interval (referred to as generation interval in the study)	Average number of days between the date of symptom onset in the source case and in the secondary case. Data on symptom onset obtained from the cases' Municipal Health Service records.	Three clusters (groups of related cases) identified, with 19, 12 and 9 cases. Overall mean serial interval time: 2.7 days (SD: 1.1 days, n=32) Mean serial interval time by cluster: • n=13 of the 19 case cluster: 2.5 days (SD: 0.9 days) • n=8 of the 12 case cluster = 3.1 days (SD: 1.1 days) • n=5 of the 9 case cluster = 2.8 days (SD: 1.7 days)
McBryde and others, 2009 (3)	Australia, May to June 2009	Retrospective cohort	n=897 influenza A(H1N1)v cases of which n=750 had data on people they had come into contact with and n=37 had an identified primary contact.	Described as laboratory-confirmed, but specific diagnostic method not provided.	Serial interval (referred to as generation interval in the study)	Defined as the time between onset of symptoms in case A to the onset of symptoms in case B, given the assumption that case A	Mean serial interval time: 2.9 days (SD: 1.4 days)

Study	Country, time period	Study type (design)	Demographics (participant number, age, sex, influenza subtype)	Laboratory diagnosis method	Outcome	Outcome measurement	Findings
			Data on age and sex not reported.			infected case B. Parametric analyses with Gamma (alpha, beta) distribution. Specific method of establishing symptom onset not specified.	
Odaira and others, 2009 (4)	Japan, May to June 2009	Prospective cohort	n=97 influenza A(H1N1)v index cases. Median age: 17 years (age range: 1 to 53 years), 41.0% female, 92% of index cases received antiviral medication. n=171 household contacts without antiviral prophylaxis. Median age: 39 years (age range: 0 to 83 years), 47.0% female. n=122 household contacts with antiviral prophylaxis. Median age: 45 years (age range: 2 to 85 years), 53% female.	RT-PCR	Serial interval	The interval from symptom onset in index case to symptom onset in household contact. Daily follow up of household contacts of index cases for approximately 8 days. Specific method of establishing symptom onset not specified.	Median serial interval time for n=14 household contacts who developed H1N1v and their n=13 respective index cases: 3 days (range between 1 and 5 days) Distribution of serial interval: • 1 day: n=1 confirmed case • 2 days: n=2 confirmed cases, n=1 suspected case • 3 days: n=7 confirmed cases • 4 days: n=1 confirmed case, n=1 suspected case • 5 days: n=1 confirmed case
Tom and others, 2011 (5)	UK, May to July 2009	Retrospective cohort	n=323 influenza A(H1N1)v cases from England's Health Protection Agency national influenza database (FluZone) with a known date of onset of symptoms and some information available on the timing of exposure. Mean (SD) age: 20.7 years (14.7 years). 50.2% female. n=63 influenza A(H1N1)v cases from other sources including regional HPA units and Health Protection	Described as laboratory-confirmed, but specific diagnostic method not provided.	Incubation period	Parametric time to event analyses of data on onset of symptoms and exposure dates, accounting for interval censoring. Subgroup analyses in those aged less than 15 years and 15 years or older. Data on symptom onset obtained from public health databases containing outbreak reporting details.	Two different distributions (Weibull and gamma) were used to model the estimated incubation times, producing 2 sets of results. Mean incubation time estimates (Weibull distribution) incubation time estimates: • n=72 participants where exact incubation times known: 2.519 days (SD: 2.113 days) • n=131 participants where exact incubation times known, or incubation times were interval censored (fell within a known interval): 2.473 days (SD: 2.009 days) • n=310 participants where exact incubation times known or were interval censored or left censored

Study	Country, time period	Study type (design)	Demographics (participant number, age, sex, influenza subtype)	Laboratory diagnosis method	Outcome	Outcome measurement	Findings
			Scotland. Mean (SD) age: 22.7 years (12.9 years). 50.8% female. Of which n=335 of 386 had sufficient data to be included in the analyses.				(known to be shorter than a specific length of time): 1.383 days (SD: 1.700 days) • n=335 participants (all participants including those where exact incubation times known, incubation times interval or left censored, or incubation times right censored (known to be longer than a specific length of time): 1.661 days (SD: 2.021 days, 95% CI 1.420 to 1.902 days) • n=132 participants aged less than 15 years: 1.244 days (SD: 2.484 days) • n=203 participants aged 15 years or older: 1.931 days (SD: 1.988 days) • median incubation time all n=335 participants: 0.963 (95% CI 0.765 to 1.174), corresponding 95th percentiles: 5.653 days (95% CI 4.759 to 6.832) Gamma distribution incubation time estimates produced similar results (this distribution was reported as slightly less appropriate by authors, therefore only Weibull distribution figures reported in text). Mean gamma distribution incubation time estimates: • n=72 participants where exact incubation times known: 2.517 days (SD: 1.932 days) • n=131 participants where exact incubation times known or incubation times were interval censored (fell within a known interval): 2.475 days (SD: 1.886 days) • n=310 participants where exact incubation times known or were interval censored or left censored (known to be shorter than a specific length of time): 1.372 days (SD: 1.684 days) • n=335 participants (all participants including those where exact incubation times known, incubation times interval or left censored, or incubation times right censored (known to be longer than a specific

Study	Country, time period	Study type (design)	Demographics (participant number, age, sex, influenza subtype)	Laboratory diagnosis method	Outcome	Outcome measurement	Findings
							length of time): 1.647 days (SD: 1.987 days, 95% CI 1.408 to 1.886 days) • n=132 participants aged less than 15 years: 1.145 days (SD: 2.164 days) • n=203 participants aged 15 years or older: 1.936 days (SD: 1.923 days) • median incubation time all n=335 participants: 0.948 days (95% CI: 0.717 to 1.158 days), corresponding 95th percentiles: 5.646 days (95% CI: 4.889 to 7.003 days) Comparison of those aged under 15 years and 15 and over: • Mean differences from the Weibull and gamma models: 0.688 (95% CI: 0.129 to 1.246) and 0.792 (95% CI: 0.284 to 1.300) days, respectively (p=0.02), longer mean incubation time in the older age group

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation heath secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Prepared by Stefano Brini, Naomi Carter, Tamsyn Harris, Jennifer Hill, Katie Kerr, and Serena Carville

For queries relating to this document, please contact: enquiries@ukhsa.gov.uk

Published: October 2024
Published reference: GOV-17336