UK Health Security Agency

Infectious and incubation period, and pre-symptomatic and asymptomatic transmission of influenza A H1N1pdm09 subtype

A rapid evidence summary

Contents

Main messages

1. This rapid evidence review summarises available evidence on the infectious period (the timeframe in which an individual may transmit the infection to others) and incubation period (the time between contracting an infection and symptom onset) as well as evidence on pre-symptomatic and asymptomatic transmission and location of exposure of influenza A subtype (H1N1pdm09).

2. Twenty-six studies were included. There were 4 cross-sectional, 18 prospective and 4 retrospective cohort studies. There were 2 studies conducted in the UK, 5 in Europe, 7 in North America, 2 in South America, one in Africa, 8 in Asia and one across multiple continents globally.

3. The primary outcomes for this review were infectious period (measured by time to viral clearance, viral load over time, culture positivity over time, serial interval, generation time) and incubation period. The secondary outcome was transmission of the virus from people who are pre-symptomatic or asymptomatic, and location of exposure.

4. Studies used different measures to assess outcomes and different summary statistics. These have been grouped by outcome in the main messages, stating which measure was used, and tables are provided in the body of the report.

5. Fourteen studies reported time to viral clearance in both children and adults. Generally, the median time to viral clearance reported in people without a known medical condition was 6 days, with individual responses ranging from one to 19 days across studies.

6. In people with influenza symptoms the mean time to viral clearance was 4.97 days (standard deviation (SD) of 2.93) compared to 3.16 days (SD: 2.12) in those without influenza symptoms. In those with a pre-existing medical condition time to viral clearance was 12 days (range: 7 to 19). In patients with pneumonia the mean time to viral clearance was 15.4 (SD: 9.0) days compared to 7.5 days (SD: 3.4) in people without pneumonia.

7. Viral load was investigated in 6 studies and was highest at symptom onset or the following few days and generally decreased over time reaching undetectable levels by day 13 to 17 after infection. Significant reductions in viral load were observed at day 6 to 8. Studies did not specifically assess whether viral load predicted rate of transmission and therefore, it was difficult to know whether higher viral load is associated with a higher risk of transmitting the virus.

8. Culture positivity over time (3 studies) showed undetectable levels of virus by day 4 or 5 since the first positive test, although in one study some people were still showing positive viral cultures up to 13 days since symptom onset.

9. Studies assessing serial interval and generation times used these terms interchangeably but reported that the average time from symptoms starting in one person to symptoms starting in someone they had infected was between 2 to 4 days.

10. The average incubation period was between 1.4 days (95% confidence intervals: 1.0 to 1.8) and 4.3 days (95% confidence intervals: 2.6 to 6.6) with the range reported across studies being between 0 and 8 days.

11. None of the included studies reported transmission of the virus from pre-symptomatic or asymptomatic people. Eight studies reported the location of outbreaks. Six of these were in schools, one of which noted the school children had travelled. One study documented transmission at a university, and 2 were in households.

12. Some studies had methodological limitations including but not limited to small sample sizes and not specifying what methods were used to select participants which could lead to risk of bias in the outcomes reported. Some people also had received antiviral treatment which could have affected viral load in the blood limiting the extent to which the reported viral load across studies can be generalised.

13. Estimates of infectious and incubation period varied across outcomes used. Overall, the evidence suggested the median time to viral clearance was around 4 to 6.2 days (although this may be slightly longer in children and in people with a weakened immune system and pneumonia). Across all studies viral load was generally highest at symptom onset or the following few days, and then gradually declined up to 13 to 20 days but decreased significantly from day 6 to 8. For culture positivity the average time from first test to a negative test was 4.5 days, and the mean timeframe between symptom onset in one person and symptoms starting in another was 2 to 4 days. The evidence suggests the incubation period averaged between 1.4 and 4.3 days but individual ranges suggested it could be as many as 8 days.

Purpose

The purpose of this rapid evidence summary was to identify and summarise the available evidence on the infectious period and incubation period as well as the evidence for evidence of pre-symptomatic or asymptomatic transmission and location of exposure of influenza A H1N1pdm09 subtype.

Methods

The review questions were:

1. What are the infectious period and incubation period of influenza A (H1N1pdm09) in humans?
2. What is the evidence of pre-symptomatic and asymptomatic transmission and location of exposure (the place where someone came into contact with influenza A (H1N1pdm09)) reported within the included studies?
    a. These were secondary outcomes and only extracted if studies had the primary outcomes.

We searched Ovid Medline and Ovid Embase for literature published from 1 January 2009 up to 31 July 2024.

Screening on title and abstracts was undertaken in duplicate by 2 reviewers for 10% of the total number of records retrieved from the initial search after deduplication with the remaining completed by one reviewer. Screening on full text was undertaken by one reviewer and excluded studies were checked by a second reviewer. Disagreement was resolved by discussion.

A protocol was produced before the literature search was conducted, including the review question, the eligibility criteria, and all other methods. Full details of the methodology are provided in the protocol in Annexe D. There were no deviations from the protocol.

The review was limited to studies including people who had laboratory-confirmed Influenza A (H1N1pdm09).

For this rapid evidence summary, the following definitions were used:

- infectious period: the timeframe when an individual may transmit the infection to others
- incubation period: the time between contracting an infection and symptom onset
- serial interval: time interval between symptom onset of the index and secondary cases
- generation time: the time between disease onset in index and secondary cases.

Evidence

In total, 4,346 studies were screened on title and abstract, of which 102 studies were screened on full text, and 26 were included in this evidence summary. The PRISMA diagram showing the flow of studies through this review is available in Annexe B. Studies excluded on full text screening are available with the reasons why in Annexe C. Full details of included studies are available are available in Annexe D.

Some studies included children aged 19 years or below only (1), others included adults only (2, 3) or both children and adults (4 to 10), while the remaining studies did not report ages. There were 2 studies conducted in the United Kingdom (8, 9), 5 studies in Europe (1, 2, 11 to 13), 7 in North America (4, 6, 10, 14 to 17), 2 in South America (5, 18), one in Africa (19), 8 in Asia (3, 7, 20-25), and one across multiple countries globally (26).

Studies used different measures to assess outcomes and different summary statistics. These have been grouped by outcome below, with tables provided for clarity detailing which measures and statistics have been used.

Primary outcomes

Infectious period

Time to viral clearance

Table 1. Characteristics of studies reporting the median

Study	Study type	Population	Median time to viral clearance	Standard deviation	Range
(4) Bhattarai (2011)	Prospective cohort	26 children and adults	6 days	Not reported	1 to 13 days
(7) Jia (2011)	Prospective cohort	67 children and adults	6 days	Not reported	4 to 10 days
(8) Killingley (2010)	Prospective cohort	19 children and adults	Whole sample: 6.2 days	Not reported	3 to 10 days
(26) Roosenhoff (2020)	Prospective cohort	683 children	9.9 to 11.5 days in those under 5 years old 7.2 to 9.0 days in those over 5 years old	Not reported	Not reported
(1) Esposito (2011)	Prospective cohort	74 children	Not reported	Not reported	3 to 17 days
(25) Yan (2012)	Prospective cohort	170 children	Not reported	Not reported	0 and 5 days
(3) Li (2010)	Prospective cohort	15 adults on long-term haemodialysis	12 days	Not reported	7 to 19 days
(2) Fraaij (2015)	Prospective cohort	15 adults with weakened immune system	Not reported	Not reported	12 to 15 days
(24) Wu (2012)	Prospective cohort	18 hospitalised adults	Not reported	Not reported	2 to 7 days
(19) Waiboci (2011)	Prospective cohort	106 children and adults	8 days	Not reported	7 to 10 days

Table 2. Characteristics of studies reporting the mean

Study	Study design	Population	Mean time to viral clearance	Standard deviation	Range
(12) Meschi (2011)	Retrospective cohort study	39 adults	People with pneumonia 15.4 days	9.0 days	Not reported
			People without pneumonia: 7.5 days	3.4 days	
(17) Wang (2017)	Prospective cohort	97 adults	With symptoms: 4.97	2.93 days	Not reported
			Without symptoms 3.16 days	2.12 days	
(14) Loeb (2012)	Prospective cohort	97 (age not reported)	Whole sample: 4.8 days	2.9 days	1 to 15 days
			Asymptomatic people: 3.2 days	2.2 days	Not reported

The time to viral clearance was investigated by 12 prospective cohort studies (1 to 4, 7, 8, 14, 17, 19, 24 to 26), and one retrospective cohort study (12). Studies measured the time between symptom onset to a negative or undetectable reverse transcription polymerase chain reaction (RT-PCR) test as a measure of time to viral clearance.

Three prospective cohort studies reported median time to viral clearance at around 6 days in samples including a mix of children and adults without a known medical condition (4, 7, 8). In the first study including 67 people with a median age of 23.7 years (range: 17 to 34), the median time between the start of symptoms and an undetectable test result was 6 days (range: 4 to 10 days) with no cases showing a positive test result after 11 days; people with comorbid conditions such as obesity or those on antiviral therapy were excluded from this study (7).

In the third study of a sample of 26 students and staff (age range: 2 to 45 years) from an elementary school experiencing an outbreak, the median time to viral clearance was 6 days (range 1 to 13 days) from the onset of fever (4).There were no statistical differences in time to viral clearance between younger children and adults (p=0.3), or between different age groups (p=0.4) in this study. More details from this study on time to viral clearance in specific age groups are presented in Annexe D.

A larger prospective cohort study in Kenya including a mixed sample of 106 children and adults (median age 6 years old, ranging from 4 months to 41 years), reported the median number of days until a negative test as 8 (95% confidence interval: 7 to 10) since symptom onset (19).

A further prospective cohort study including 683 children under the age of 13 years reported that the median time for viral clearance ranged from 9.9 to 11.5 days for children under 5 years of age and for children above the age of 5 years range for the same outcome was 7.2 to 9.0 days (26). Another study including 74 children with an average age of 5.2 years (SD: 4.9) and no known medical conditions, showed that all children had detectable virus by day 3 after disease onset, which gradually decreased over time until day 17 when no children had detectable virus load (1). In 170 middle school-aged children, initial virus detection was found 2 days before symptom onset and the majority of viral clearance occurred between 0 and 5 days after symptom onset (25). The peak of virus shedding happened on the day of symptom onset followed by a steady decrease over the next 8 days (p=0.026) (25).

In one prospective cohort study of 97 people from the Hutterite community in Canada, whose age was not reported, the mean time to viral clearance since testing for the total sample was 4.8 days (SD: 2.9 days; range: 1 to 15 days) and for asymptomatic individuals, it was 3.2 days (SD: 2.2 days) (14). Individuals were swabbed if they reported influenza symptoms during twice weekly research visits, and asymptomatic individuals were swabbed during confirmed influenza outbreaks. In this study no additional demographic details were reported (14).

Another prospective cohort study compared time to viral clearance in 97 people with and without influenza symptoms (12% [12 of 97] were asymptomatic, 25% were over 16 years old). They reported that the mean time to viral clearance since the first test was significantly longer (p=0.02) in people with influenza symptoms (mean 4.97 days [SD: 2.93]) compared to 3.16 days (SD: 2.12) in those without influenza symptoms (17). The study did not report a mean time for the whole group.

One retrospective cohort study compared the time to a negative test in 39 people with a median age of 51 years who had been hospitalised for H1N1 with pneumonia (11 people) to those without pneumonia (28 people) (12). The study reported the mean number of days until a negative test from symptom onset (used to inform time to viral clearance) was 15.4 (SD: 9.0) in people who had pneumonia, compared to 7.5 days (SD: 3.4) in those without pneumonia (12). Viral clearance took longer in those with pneumonia compared to those without pneumonia (p=0.002) but the time frame was not stated (12).

Three other prospective cohort studies included specific populations with pre-existing medical conditions. One study including 15 people on long-term haemodialysis with a mean age of 47.6 years (SD: 22.0), reported the median duration of a RT-PCR positive test (which informs time to viral clearance) as 12 days (range: 7 to 19) (3). In another study including 15 people (median age 52 years) with a weakened immune system, 14 people had a negative test result by day 15 after they had a positive test result, though many had negative test results sooner than that (2). It is worth noting however, that not only was the sample in both of these studies small, in the second study some people had not been tested every day, negatively impacting on the accuracy and precision of the outcome (2). The third study included 18 people hospitalised because of complications due to having the virus. Patients were categorised as 'complicated' for reasons such as requiring mechanical ventilation or with pneumonia (mean age 42, compared to an 'uncomplicated' group with a mean age of 26.8). Peak viral clearance occurred within 2 days of symptom onset in both groups. Viral clearance was slower in the complicated group, but both groups had undetectable viral ribonucleic acid (RNA) by day 7 after symptom onset (24).

Time to viral clearance summary

Overall, the evidence seems to suggest time to viral clearance averages around 4 to 6.2 days (although this may be slightly longer in children and in people with a weakened immune system and pneumonia). The range of individual responses in some studies was as little as one day up to as many as 19 days. Some of the wider ranges observed across studies especially in those using the RT – PCR may be due to studies having recruited small numbers of people which decreases the precision of the time frame indicating viral clearance.

Viral load over time

Table 3. Characteristics of studies reporting the mean viral load

Study	Study type	Population	Mean viral load (log_{10} copies per millilitre)	Standard deviation
(1) Esposito (2011)	Prospective cohort	74 children	Day 1 and 2: 8.19	1.41
			Day 7: 3.90	2.83
			Day 13 to 17: below 1	1.66
			Day 17: 0	0
(14) Loeb (2012)	Prospective cohort	97 adults	Not reported (see narrative summary)	Not reported
(18) Rodrigues Guimaraes Alves (2020)	Cross-sectional	71 symptomatic adults	1 to 2 days after symptom onset: 7.07	1.54
			5 to 8 days after symptom onset: 6.43	2.48

Table 4. Characteristics of studies reporting the median viral load

Study	Study type	Population	Median viral load (No units of measurement reported)	Interquartile range
(11) Gianella (2011)	Prospective cohort	58 older adults (65 years and older)	At day 0 since diagnosis for 58 patients: 0.1	0.02 to 2.0
			At day 8 since diagnosis for 10 people: 0.01	0.002 to 0.17
			At day 16 since diagnosis for 1 person: 0.0003	Not reported
(5) Gorini da Veiga (2012)	Cross-sectional	198 adults	At day 0 from symptom onset: 7.3	0.2 to 180.1
			At day 1 from symptom onset: 14.3	0.6 to 161.2
			At day 2 from symptom onset: 20.32	2.3 to 221.1
			At day 5 or more from symptom onset: 0.6	0.1 to 14.6

Table 5. Characteristics of studies reporting the mean geometric viral load

Study	Study type	Population	Mean geometric viral load (log_{10})	Not reported
(20) Ip (2015)	Prospective cohort	33 adults	1 to 2 days before illness onset: 2.7	Not reported
			1 to 2 days after illness onset: 4.5	

Viral load over time was investigated in 4 prospective cohort studies (1, 11, 14, 20) and 2 retrospective cross-sectional studies (5, 18). Many of these studies measured viral load in decimal logarithms (log_{10}) with higher values indicating higher viral load and lower values indicating lower viral load. These studies did not assess whether viral load is associated with risk of transmitting the virus and therefore while higher viral load may suggest greater likelihood of an individual being infectious, it was not possible to determine from these studies whether it is associated with risk of transmission.

In one prospective cohort study, viral load was measured over 17 days (1). In this study, mean viral load between day one and 2 was 8.19 (SD: 1.41) log_{10} copies per millilitre. By day 7 the viral load had dropped to 3.90 (SD: 2.83) log_{10} copies per millilitre with about 57% of children clearing the virus. By days 13 to 17 the viral load had dropped to below 1 (SD: 1.66) log_{10} copies per millilitre with fewer than 20% of children clearing the virus. At day 17 no children were clearing the virus (1).

In another prospective cohort study including 58 older adults aged 65 years and older, the median relative viral load at day 0 (since diagnosis) was 0.1 (interquartile range: 0.02 to 2.0) for the whole sample. By day 8, the median relative viral load was 0.01 (IQR 0.002 to 0.17) in 10 people (11). By day 16, the study reported that only one person had a viral load of 0.0003. A further prospective cohort study of 33 people living in the community reported the mean geometric viral load was 2.7 log_{10} one to 2 days before the onset of acute respiratory illness, and 4.5 one to 2 days after the onset of acute respiratory illness (20). One prospective cohort study reported that in 97 people viral load was highest around the onset of acute respiratory illness and declined by day 8 with participants clearing the virus until day 14 but no further specific values or details were reported (14).

One retrospective cross-sectional study including 198 patients reported the relative median viral load from day 0 to day 5 or more from the onset of symptoms. The median viral load on day 0 was 7.3 (IQR: 0.2 to 180.1). This rose to 14.3 (IQR: 0.6 to 161.2) on day one, by day 2 median viral load reached its peak at 20.32 (IQR: 2.3 to 221.1) and then dropped to 0.6 (0.1 to 14.6) by day 5 or more (5). This study did not report a unit of measurement for viral load over time (5). In another retrospective cross-sectional study including 71 outpatients who were symptomatic, the mean viral load reported one to 2 days after symptom onset was 7.07 RNA copies per millilitre (SD: 1.54) which dropped to 6.43 (SD: 2.48) 5 to 8 days after symptom onset (18).

Viral load over time summary

Across all studies viral load was generally highest at symptom onset or the following few days, and then gradually declined up to 13 to 20 days. Since studies used different measurements to assess viral load and reported the median, arithmetic mean, geometric mean, or log_{10}, it is not possible to directly compare or synthesise the evidence. Two of the studies retrospectively assessed symptom onset (for example, date of symptom onset) and as such, people may not have accurately remembered when they first started experiencing symptoms increasing the risk of recall bias.

Culture positivity over time

Table 6. Characteristics of studies reporting the proportion of people with a positive viral culture

Study	Study type	Population	Proportion with a positive culture
(19) Waiboci (2011)	Prospective cohort	85 children and adults (mostly children)	At day 0 to 3 after symptom onset: 95% (81 of 85) At day 11 onwards after symptom onset: 18% (3 of 17)
(9) Killingley (2016)	Prospective cohort	39 hospitalised cases (age not reported)	At day 5 after symptom onset: 26% (10 of 39)

Table 7. Characteristics of studies reporting the mean duration of culture positivity

Study	Study type	Population	Mean duration of culture positivity	Range
(9) Killingley (2016)	Prospective cohort	39 hospitalised cases (age not reported)	4.6 days	3 to 10 days
(8) Killingley (2010)	Prospective cohort	12 children and adults	4.7 days	3 to 8 days

Three prospective cohort studies reported culture positivity over time (8, 9, 19). One study included 140 cases and took repeated swabs from the nose and mouth every 2 days until the person had 2 negative RT-PCR tests in a row. Samples were cultured where possible; 85 out of the 140 cases completed the study. People taking part in the study ranged in age from 4 months to 41 years, and most were children (median age was 6 years). The proportion of people with a positive viral culture after symptom onset reduced over time where 95% (81 of 85) had a positive culture on days 0 to 3 after symptom onset, 93% (37 of 40) on days 4 to 7, 55% on days 8 to 10 (11 of 20), and 18% (3 of 17) from day 11 onwards (19). The longest time after symptom onset when virus was cultured was 13 days (3 cases had virus cultured for 11 days or more, but it was unclear how many of those reached 13 days).

In another study including 39 hospitalised cases, for whom age and sex was not reported (9), the mean duration of culture positivity was 4.6 days (interquartile range: 4 to 5 days, range 3 to 10 days), and 26% (10 of 39) of people produced live virus for at least 5 days from the onset of illness. It is unclear why the study reported an interquartile range as the measure of variance for mean duration of culture positivity. It is possible that the distribution of the data was skewed, in which case median duration of culture positivity might have better represented the average. As the cases in this cohort were hospitalised, it is possible they were more unwell on average than cases in the community, which could alter viral dynamics such as culture positivity over time.

A further study followed 19 H1N1pdm09 cases from hospital and community settings over time. Participants ages ranged from less than 1 year to 34 years old, and the median age was 12 years. For 12 cases where culture results were available, the mean duration of culture positivity was 4.7 days (range 3 to 8 days). This estimate was lower, at 2.9 days (range 0 to 8 days), when 6 cases with a negative culture result (but positive RT-PCR result) were also included in the analysis (8).

Culture positivity over time summary

The evidence on culture positivity over time in studies including a mix of children and adults showed the mean duration of culture positivity was about 4 and a half days ranging between 0 and 10 days. Also, the proportion of people testing negative for the virus gradually increased across time with most people (about 80%) testing negative after day 11 with a few still testing positive at day 13. Therefore, the evidence seems to suggest presence of the virus by culture may be detected for up to 2 weeks.

Serial interval

Table 8. Characteristics of studies reporting the median serial interval

Study	Study type	Population	Median serial interval	95% confidence interval
(6) Janjua (2012)	Cross-sectional	Children and adults in a school outbreak Number unclear	4.2 days	1.6 to 9.8 days
(10) Lessler (2009)	Cross-sectional	Children and adults in a school outbreak Number unclear	2.7 days	2.0 to 3.5 days

Table 9. Characteristics of studies reporting the mean serial interval

Study	Study type	Population	Mean serial interval	95% confidence interval	Standard deviation
(15) Petrie (2013)	Prospective cohort	5 transmission pairs in households (age not reported)	2.8 days	1.3 to 5.0 days	Not reported
(21) Roll (2011)	Retrospective cohort	Cases from the National Influenza Center (age not reported) Number unclear	2.9 days	Not reported	1.8 days
(13) Suess (2012)	Prospective cohort	19 transmission pairs, mostly children	2.4 days	Not reported	1.5 days

Five studies reported serial interval between index and secondary cases. These included 2 prospective cohort studies (13, 15), one retrospective cohort study (21), and 2 cross-sectional studies (6, 10). For 2 of these studies, the authors described the outcome as generation time rather than serial interval, however as they used patient-reported disease onset, these were considered to represent serial interval (10, 21).

One cross-sectional study was a survey conducted in children from a school affected by the virus in rural Canada, and Aboriginal on-reserve residents in the same area. This study reported a median serial interval of 4.2 days (95% confidence interval: 1.6 to 9.8) when only including transmissions between laboratory-confirmed cases (6). In another cross-sectional survey during an outbreak in a school, the median serial interval was reported to be 2.7 days (95% confidence interval: 2.0 to 3.5 days) (10). For both studies, the number of transmission pairs on which the analyses were based was unclear.

In one prospective cohort study amongst 328 households within a local healthcare system in the USA, there were 5 confirmed transmission pairs of H1N1pdm09. The mean serial interval was reported to be 2.8 days (95% confidence interval: 1.3 to 5.0 days) based on those 5 transmissions (15). In another prospective cohort study, which was embedded in a randomised controlled trial, the mean serial interval was reported as 2.4 days (SD: 1.5 days), based on 19 transmission pairs (13).

One retrospective cohort study used a database of confirmed cases from the National Influenza Centre in Israel (21). This study reported the mean serial interval as 2.9 days (SD: 1.8 days), though the number of transmission pairs on which the analysis was based was unclear (21).

Serial interval summary

Across the 5 studies the most likely estimates of serial interval were represented by averages such as the means and medians, which fell between 2 and 4 days. However, the measures of uncertainty around those estimates suggested the serial interval might fall anywhere between one and 10 days. As serial interval is the time from symptoms starting in an index case to symptoms starting in a case that they infect, measuring it generally requires transmission pairs. The relevant sample size is therefore the number of transmissions between index and secondary cases that were included in the analysis. Across the studies this sample size was either small, or not reported.

Incubation period

Table 10. Characteristics of studies reporting the median incubation period

Study	Study type	Population	Median incubation period	Range
(22) Uchida (2013)	Prospective cohort	324 participants (no age details available)	2 days	0 to 8
(3) Li (2010)	Prospective cohort	15 adults undergoing chronic haemodialysis	4 days	1 to 7

Table 11. Characteristics of studies reporting the mean incubation period

Study	Study type	Population	Mean incubation period	95% confidence interval
(10) Lessler (2009)	Cross-sectional	124 children and adults	1.4 days	1.0 to 1.8 1.7 to 2.6
(16) Tuite (2010)	Retrospective cohort	316 young adults	4.3 days	2.6 to 6.6
(23) Wang (2012)		79 children and adults	1.6 days	1.2 to 2.3

There was one cross-sectional study (10), 2 retrospective cohort studies (16, 23), and 2 prospective cohort studies (3, 22) investigating incubation period.

One cross-sectional study in the USA included 124 people in a high school (97% students with a median age of 16, ranging between 14 and 19 and for adults the median age was 25 years ranging between 20 to 47 years). The mean incubation period was reported as 1.4 days (95% confidence intervals: 1.0 to 1.8) with the majority of people (95%) experiencing symptoms within 2.2 days (95% confidence intervals: 1.7 to 2.6) (10). These results were from participants who responded to an online survey, which introduces the possibility of self-report bias.

One retrospective cohort study in Canada of 316 young adults with a mean age of 21.9 years (SD: 15.7) a mean incubation time was 4.3 days (95% confidence intervals: 2.6 to 6.6) (16). The study initially recruited 3,152 people but data to calculate incubation period was only available for 316 people. No further details such as demographic or clinical factors were reported in this study. A second retrospective cohort study in China with 79 cases amongst students and staff from a middle-school reported mean incubation time was 1.6 days (95% confidence intervals: 1.2 to 2.3) and the shortest and longest incubation times were 0.4 and 4.2 days respectively (23).

One prospective cohort study reported the median incubation time was 2 days (range: 0 to 8) in 324 people (no demographic details reported except for sex including 208 males 116 females) (22). A second prospective cohort study reported it to be 4 days (range: 1 to 7) in people on long term haemodialysis mean age 47.6 years (SD: 22.0 years), 60% of whom were men (3). In this study, all participants also received oseltamivir, which may have had an impact on incubation time.

Incubation period summary

The evidence suggests the incubation period averages between 1.4 and 4.3 days but individual ranges varied up to be as many as 8 days. This wide range may be due to studies including people with or without known medical conditions and that symptom onset was likely self-reported which can introduce self-report bias (although how symptoms onset was measured was not always specifically described in the study).

Secondary outcomes

Location of exposure

Nine of the included studies reported location of exposure for H1N1pdm09 cases. In 6 studies, cases occurred in educational settings, including outbreaks in a primary and middle school in China (25) a middle school in China (23), an elementary school in rural Canada (6), an elementary school in the USA (4), a high school in the USA (10), and a university in Japan (22). In the outbreak occurring in a high school in the USA, 14 students reported a recent travel history to Mexico (4). In another 2 studies from the USA and Hong Kong, transmission took place in the context of households (15, 20).

Secondary attack rate from asymptomatic or pre-symptomatic index cases

None of the included studies reported on secondary attack rates that could inform whether there was transmission from people who were pre-symptomatic or asymptomatic.

Health inequalities

There was limited evidence on health inequalities in relation to the review question. Studies did not routinely report demographic or clinical details and therefore it was not possible to explore whether the outcomes in this review differed depending on cultural variations or differences between ethnic or social groups. There was some evidence suggesting the median time for viral clearance was slightly longer in children and young people compared to that reported in adults. There was also some evidence suggesting that the time between a positive and negative test was longer in people with pre-existing health conditions or with a weakened immune system.

Limitations

This rapid evidence summary used streamlined systematic methods to accelerate the review process. Most article screening was completed without duplication. A narrower range of databases were searched and screened, and grey literature was excluded, therefore it is possible relevant studies may have been missed. Due to time constraints critical appraisal was not undertaken which limits our ability to interpret the findings in the context of risk of bias.

There were several methodological limitations across studies such as small sample sizes and a lack of adjustment for confounding factors that may have influenced the outcome estimates in the studies and may limit the extent to which results can be generalised to the wider population.

Studies also did not assess whether viral load was associated with risk of transmitting the virus and therefore, from the evidence in this review, it was not possible to know whether different levels of viral load in those with the virus may lead to increased transmission of the virus. Studies also used different measurements in assessing viral load including averages, geometric average, and $\log_{10}$ making it difficult to compare different values of viral load across studies. Additionally, some people in some of the studies had received antiviral medications (which was not adjusted for in statistical analyses) which can affect the amount of virus circulating in the blood and limited the extent to which viral load in these people is representative of the viral load in the untreated population with this virus.

This review included studies that had laboratory-confirmed H1N1pdm09, which strengthens confidence participants in the study were infected with this specific influenza A subtype. However, it is worth noting that laboratory-confirmed cases only reflect a subset of the whole

population infected with the virus and therefore study findings may not represent the whole population with this virus.

Evidence gaps

There were a limited number of studies investigating culture positivity over time and generation time making it problematic to draw conclusions about infectious period from these 2 outcomes. Some studies measured the time between symptom onset in one case and symptom onset in cases they had transmitted the infection to (serial interval), however the time of symptom onset may not reflect the time at which the person was infected. No studies directly measured transmission between cases from the point of infection.

Conclusion

Primary outcomes

Infectious period

The time to viral clearance since symptoms onset or a negative RT-PCR test across studies in people without a known medical condition was generally reported as a median of 6 days (range: 1 to 19). The mean time to viral clearance in people experiencing influenza symptoms was 4.97 days (SD: 2.93) compared to 3.16 days (SD: 2.12) in those who did not experience influenza symptoms but the mean time to viral clearance in people with pneumonia was even longer at 15.4 (SD: 9.0) days compared to 7.5 days (SD: 3.4) in people without pneumonia. People with known medical conditions appeared to have the longest time to viral clearance at 12 days (range: 7 to 19). Studies adopted different methodologies and recruited people of different ages (children, adults, or a mix of both) and clinical profiles meaning synthesis of study results was not possible, but in general, the evidence seems to suggest time to viral clearance averages around 4 to 6.2 days, although this may be slightly longer in children and in people with a weakened immune system and pneumonia.

Studies assessing viral load over time used different measures of viral load including average, median, and the geometric mean with one study not reporting the unit of measurement, which limits comparison and synthesis across studies. However, studies were generally consistent indicating a similar trend showing of viral load over time decreasing with the proportion of people testing negative for the virus increasing. This would seem to suggest viral load over time may have been associated with resolution of symptoms with highest viral load values at symptom onset. Nonetheless, viral load over time decreased close to undetectable levels by day 13 to 17 since infection, although significant reduction in viral load was observed at around 6 to 8 days since infection.

There was limited evidence using culture positivity over time. However, where available it tended to show that the proportion of people with positive viral cultures declined over time, with most people still showing positive cultures after 4 to 5 days but with some still showing positive viral cultures up to 13 days since symptom onset.

For serial interval and generation time, a limited number of studies used these terms interchangeably to mean the time it takes symptoms in one person to develop to symptoms starting in someone else whom they had infected. the most likely estimates of serial interval were represented by averages such as the means and medians, which fell between 2 and 4 days. However, the measures of uncertainty around those estimates suggested the serial interval might fall anywhere between one and 10 days. Studies indicate this time frame ranged between 2 and 4 days but extending to one to 10 days when measures of uncertainty were taken into account. Small sample sizes in these studies likely produced imprecise estimates and could explain the large variation in the time it takes for one person to infect another person.

Incubation period

The evidence-base indicated the mean incubation period for laboratory-confirmed H1N1pdm09 ranged between 2 to 6 days but individual ranges in some studies indicated incubation period may be as much as 8 days. However, this range was derived from studies with different designs, different sample sizes and a wide range of ages including children and adults, some of whom had comorbidities, however, for others this was not reported. Studies did not always report additional demographic or clinical details.

Secondary outcomes

There were 6 outbreaks in schools, one at a university, and 2 outbreaks occurring in households. There were no studies reporting transmission of the virus from pre-symptomatic or asymptomatic people.

Summary

There were limitations in the evidence base, including lack of detail on how people were selected for studies, lack of adjustment for other factors which may have influenced the results (confounding factors) and self-report of some outcomes, meaning there is a risk of bias in the results and they may not be generalisable to the whole population with infection. There was also no direct evidence of transmission between cases, and most studies investigated indicators of infectious period such as viral load over time and viral clearance. While infectious period was estimated differently across studies, the median time to viral clearance around was 4 to 6.2 days and a mean culture positivity time frame of 4.5 days between the first positive test and a negative test. Higher viral load was generally noted at the start of symptoms progressively reducing to undetectable levels within 20 days with serial interval ranging between 2 to 4 days. The incubation period averaged between 1.4 and 4.3 days with some evidence suggesting 8 days for at the individual level. No study reported pre-symptomatic or asymptomatic transmission with most outbreaks occurring in schools, followed by households, and at a university.

Acknowledgments

We would like to thank colleagues within the All Hazards Public Health Response division who either reviewed or input into aspects of the review.

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References

1. Esposito S and others. 'Viral shedding in children infected by pandemic A/H1N1/2009 influenza virus' Virology Journal 2011: volume 8, page 349
2. Fraaij PL and others. 'Viral shedding and susceptibility to oseltamivir in hospitalized immunocompromised patients with influenza in the Influenza Resistance Information Study (IRIS)' Antiviral Therapy 2015: volume 20, issue 6, pages 633 to 642
3. Li H and others. 'Clinical features of 2009 pandemic influenza A (H1N1) virus infection in chronic hemodialysis patients' Blood Purification 2010: volume 30, issue 3, pages 172 to 177
4. Bhattarai A and others. 'Viral shedding duration of pandemic influenza A H1N1 virus during an elementary school outbreak: Pennsylvania, May to June 2009'. Clinical Infectious Diseases 2011: volume 52, pages S102 to S108
5. Gorini da Veiga AB and others. 'Viral load and epidemiological profile of patients infected by pandemic influenza a (H1N1) 2009 and seasonal influenza a virus in Southern Brazil' Journal of Medical Virology 2012: volume 84, issue 3, pages 371 to 379
6. Janjua NZ and others. 'Transmission dynamics and risk factors for pandemic H1N1-related illness: outbreak investigation in a rural community of British Columbia, Canada' Influenza and Other Respiratory Viruses 2012: volume 6, issue 3, pages e54 to 62
7. Jia N and others. 'Viral shedding in Chinese young adults with mild 2009 H1N1 influenza' Chinese Medical Journal 2011: volume 124, issue 10, pages 1,576 to 1,579
8. Killingley B and others. 'Virus shedding and environmental deposition of novel A (H1N1) pandemic influenza virus: interim findings' Health Technology Assessment (Winchester, England) 2010: volume 14, issue 46, pages 237 to 354
9. Killingley B and others. 'The environmental deposition of influenza virus from patients infected with influenza A(H1N1)pdm09: Implications for infection prevention and control' Journal of Infection and Public Health 2016: volume 9, issue 3, pages 278 to 288
10. Lessler J and others. 'Outbreak of 2009 pandemic influenza A (H1N1) at a New York City School' New England Journal of Medicine 2009: volume 361, pages 2,628 to 2,636
11. Giannella M and others. 'Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients'. Clinical Microbiology and Infection 2011: volume 17, issue 8, pages 1,160 to 1,165
12. Meschi S and others. 'Duration of viral shedding in hospitalized patients infected with pandemic H1N1' BMC Infectious Diseases 2011: volume 11, page 140
13. Suess T and others. 'Comparison of shedding characteristics of seasonal influenza virus (sub)types and influenza A(H1N1)pdm09; Germany, 2007-2011' PLoS ONE [Electronic Resource] 2012: volume 7, issue 12, e51653
14. Loeb M and others. 'Longitudinal study of influenza molecular viral shedding in Hutterite communities' Journal of Infectious Diseases 2012: volume 206, issue 7, pages 1,078 to 1,084
15. Petrie JG and others. 'Influenza transmission in a cohort of households with children: 2010-2011' PLoS ONE [Electronic Resource] 2013: volume 8, issue 9, e75339

16. Tuite AR and others. 'Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza' Cmaj 2010, pages 131 to 136
17. Wang B and others. 'Predictors of influenza a molecular viral shedding in Hutterite communities' Influenza and Other Respiratory Viruses 2017: volume 11, issue 3, pages 254 to 262
18. Rodrigues Guimaraes Alves V and others. 'Influenza A(H1N1)pdm09 infection and viral load analysis in patients with different clinical presentations' Memorias do Instituto Oswaldo Cruz 2020: volume 115, e200009
19. Waiboci LW and others. 'Viral shedding in patients infected with pandemic influenza A (H1N1) virus in Kenya, 2009' PLoS ONE [Electronic Resource] 2011: volume 6, issue 6, e20320
20. Ip DKM and others. 'The Dynamic Relationship between Clinical Symptomatology and Viral Shedding in Naturally Acquired Seasonal and Pandemic Influenza Virus Infections' Clinical Infectious Diseases 2015: volume 62, pages 431 to 437
21. Roll U and others. 'Onset of a pandemic: characterizing the initial phase of the swine flu (H1N1) epidemic in Israel' BMC Infectious Diseases 2011: volume 11, page 92
22. Uchida M and others. 'Evaluation of factors affecting variations in influenza A/H1N1 history in university students, Japan' Journal of Infection and Chemotherapy 2013: volume 19, issue 4, pages 665 to 672
23. Wang C and others. 'Epidemiological and clinical characteristics of the outbreak of 2009 pandemic influenza A (H1N1) at a middle school in Luoyang, China' Public Health 2012: volume 126, issue 4, pages 289 to 294
24. Wu UI and others. 'Severity of pandemic H1N1 2009 influenza virus infection may not be directly correlated with initial viral load in upper respiratory tract' Influenza and Other Respiratory Viruses 2012: volume 6, issue 5, pages 367 to 373
25. Yan L and others. 'Epidemiological and virological characteristics of pandemic influenza A (H1N1) school outbreaks in China in 2009' PLoS ONE [Electronic Resource] 2012: volume 7, issue 9, e45898
26. Roosenhoff R and others. 'Viral kinetics and resistance development in children treated with neuraminidase inhibitors: The influenza resistance information study (IRIS)' Clinical Infectious Diseases 2020: volume 71, pages 1,186 to 1,194

Annexe A. Protocol

Review question

The review question is:

1. What are the infectious period and incubation period of influenza A (H1N1pdm09) in humans, and what is the evidence of asymptomatic transmission?

This rapid evidence summary will summarise evidence on the incubation and infectious periods as well as on asymptomatic transmission of pandemic H1N1pdm09 in humans. A search for primary evidence to answer this review question will be conducted from 2009 up to 31 July 2024.

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
- serial interval: time interval between symptom onset of the index and secondary cases
- generation time: the time between disease onset in index and secondary cases.

Eligibility criteria

Table A.1 Inclusion and exclusion criteria

	Included	Excluded
Population	Humans (any age)	Any animal
Context	2009 influenza A pandemic	
Settings	Any	
Intervention or exposure	Laboratory-confirmed Influenza A (pandemic H1N1pdm09)	Other influenza Other infectious diseases
Outcomes	Primary outcomes: Any measure of incubation period of influenza A (H1N1pdm09) Any measure of infectious period of influenza A (pandemic H1N1pdm09) including the following: • transmission period • culture positivity over time	

	Included	Excluded
	• serial interval and generation time • time to viral clearance • viral load (polymerase chain reaction cycle threshold as inferred viral load) Secondary outcome (these will be extracted only from studies that have at least one of the primary outcomes): • transmission of H1N1pdm09 from people with pre-symptomatic or asymptomatic H1N1pdm09 as measured by secondary attack rates • location of exposure (for example schools, households)	
Language	English	Any other language
Date of publication	Between 2009 and 31 July 2024	Prior to 2009
Study design	Observational studies: • cohort studies • case-control studies • cross-sectional studies	Interventional or experimental trials, such as: • randomised controlled trials • non-randomised controlled trials • one-arm trials • quasi-experimental studies • cross-over trials Systematic, narrative, or scoping reviews Meta-analyses Guidelines Opinion pieces Modelling studies Laboratory studies Ecological studies Case reports Case series

	Included	Excluded
Publication type	Peer-reviewed published research	Preprints Conference abstracts Editorials Letters News articles Grey literature

Identification of studies

The following databases will be searched for studies published from 1 January 2009 up to 31 July 2024: Ovid Medline, Ovid Embase. The search strategy is presented below.

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

Where studies present data in a consistent format, a narrative synthesis will be produced to interpret the findings. The number of studies, the number of participants in each study, effect size and variance and a summary of the risk of bias across studies will be summarised and

presented. Alternatively, if studies present methodological differences that would make synthesis inappropriate, a narrative summary of each study will be provided.

Health inequalities

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

Clarifications

The research questions were clarified in the report by adding one more question reflecting the secondary outcomes.

The definition of serial interval and generation time were included in the protocol to clarify their meaning.

Search strategy

Ovid MEDLINE(R) ALL (1946 to 31 July 2024)

1. Influenza A Virus, H1N1 Subtype/ (18006)
2. h1n1*.tw,kf. (21007)
3. H1N12009.tw,kf. (7)
4. (pdm9 or pdm09).tw,kf. (1999)
5. ("(H1N1)pdm09" or "(H1N1)pdm9" or "(H1N1)pdm2009").tw,kf. (1979)
6. ("H1N1 pdm09" or "H1N1 pdm9" or "H1N1 pdm2009").tw,kf. (1979)
7. ("(H1N1) pdm09" or "(H1N1) pdm9" or "(H1N1) pdm2009").tw,kf. (1979)
8. (H1N1pdm09 or H1N1pdm9 or H1N1pdm2009).tw,kf. (538)
9. ("A/(H1N1)pdm09" or "A/(H1N1)pdm9" or "A/(H1N1)pdm2009").tw,kf. (1854)
10. ("A(H1N1)pdm09" or "A(H1N1)pdm9" or "A(H1N1)pdm2009").tw,kf. (1854)
11. AH1N1*.tw,kf. (115)
12. "A(H1N1)".tw,kf. (8702)
13. ("A/(H1N1)" or "A/H1N1").tw,kf. (8702)
14. (swine adj3 (pandemic* or flu or influenza)).tw,kf. (3858)
15. 2009 pandemic.tw,kf. (2133)
16. ("2009" adj (influenza or flu)).tw,kf. (1626)
17. ("A(H1)pdm09" or "A(H1)pdm9" or "A(H1)pdm2009").tw,kf. (25)
18. (H1pdm09 or H1pdm9 or H1pdm2009).tw,kf. (14)
19. swine H1.tw,kf. (41)
20. ("H1N1/09" or "H1N1/9" or "H1N1/2009").tw,kf. (2267)
21. or/1-20 (26520)
22. ((Transmis* or transmit*) adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (15253)

23. (Infectio* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (64802)
24. (Contagio* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (341)
25. (Isolation adj3 (duration* or time or length* or period*)).tw,kf. (3953)
26. (clearance* adj5 (duration* or time* or length* or period*)).tw,kf. (8301)
27. (viral load* adj5 (duration* or time* or length* or period*)).tw,kf. (2284)
28. cycl* threshold*.tw,kf. (2995)
29. CT value*.tw,kf. (5735)
30. (peak* adj1 (vir* load* or vir* concentrat*)).tw,kf. (435)
31. (Viral Load/ or exp Disease Transmission, Infectious/) and Time/ (42)
32. *Viral Load/ or exp *Disease Transmission, Infectious/ (52014)
33. chain of transmission.tw,kf. (422)
34. incubat*.tw,kf. (351191)
35. Infectious Disease Incubation Period/ (412)
36. Time Factors/ (1236673)
37. Time/ (14432)
38. (latent or latency).tw,kf. (200948)
39. Latent Infection/ (225)
40. (time adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (67736)
41. (period adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (17255)
42. (asymptom* adj5 (duration or period or length*)).tw,kf. (2235)
43. (generation adj3 time).tw,kf. (5935)
44. transmission.ti. (83390)
45. infectious.ti. (61477)
46. (shed* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (3867)
47. (case* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (90741)
48. virus shedding/ (4302)
49. (PCR positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (488)
50. (culture positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (451)
51. (Viral adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (11518)
52. (Virus* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (16254)
53. serial interval*.tw,kf. (460)
54. (virus adj2 amount* adj5 (duration* or time* or length* or period*)).tw,kf. (47)
55. (virus adj2 level* adj5 (duration* or time* or length* or period*)).tw,kf. (98)
56. exp Asymptomatic Diseases/ (10264)
57. or/22-56 (2201323)
58. transmiss*.tw,kf. (509581)
59. transmit*.tw,kf. (208929)
60. (breakthrough or break through).tw,kf. (31968)
61. viral load*.tw,kf. (43851)
62. viral burden.tw,kf. (1227)
63. viral level*.tw,kf. (401)
64. (shed*1 or shedding).tw,kf. (141168)
65. cytopath* effect*.tw,kf. (9084)

66. exp Disease Transmission, Infectious/ (83001)
67. Cytopathogenic Effect, Viral/ (9611)
68. or/58-67 (929235)
69. asymptomatic*.tw,kf. (199265)
70. symptomatic*.tw,kf. (236006)
71. pre-symptomatic.tw,kf. (2154)
72. non-symptomatic.tw,kf. (1098)
73. (symptom free or symptom-free).tw,kf. (9457)
74. no symptom*.tw,kf. (12378)
75. with* symptom*.tw,kf. (87384)
76. symptomless.tw,kf. (3261)
77. symptom* status.tw,kf. (1748)
78. or/69-77 (464070)
79. 68 and 78 (24731)
80. 57 or 79 (2217490)
81. 21 and 80 (3852)
82. limit 81 to yr="2009 -Current" (3426)
83. limit 81 to dt=20090101-20240731 (3431)
84. 82 or 83 (3434)

Embase (1974 to 31 July 2024)

1. exp "influenza a virus (h1n1)"/ (7681)
2. h1n1*.tw,kf. (27032)
3. h1n12009.tw,kf. (19)
4. (pdm9 or pdm09).tw,kf. (2277)
5. ("(H1N1)pdm09" or "(H1N1)pdm9" or "(H1N1)pdm2009").tw,kf. (2261)
6. ("H1N1 pdm09" or "H1N1 pdm9" or "H1N1 pdm2009").tw,kf. (2261)
7. ("(H1N1) pdm09" or "(H1N1) pdm9" or "(H1N1) pdm2009").tw,kf. (2261)
8. (H1N1pdm09 or H1N1pdm9 or H1N1pdm2009).tw,kf. (639)
9. ("A/(H1N1)pdm09" or "A/(H1N1)pdm9" or "A/(H1N1)pdm2009").tw,kf. (2107)
10. ("A(H1N1)pdm09" or "A(H1N1)pdm9" or "A(H1N1)pdm2009").tw,kf. (2107)
11. AH1N1*.tw,kf. (229)
12. "A(H1N1)".tw,kf. (10907)
13. ("A/(H1N1)" or "A/H1N1").tw,kf. (10907)
14. (swine adj3 (pandemic* or flu or influenza)).tw,kf. (4562)
15. 2009 pandemic.tw,kf. (2559)
16. ("2009" adj (influenza or flu)).tw,kf. (2010)
17. ("A(H1)pdm09" or "A(H1)pdm9" or "A(H1)pdm2009").tw,kf. (29)
18. (H1pdm09 or H1pdm9 or H1pdm2009).tw,kf. (21)
19. swine H1.tw,kf. (49)
20. ("H1N1/09" or "H1N1/9" or "H1N1/2009").tw,kf. (2780)
21. or/1-20 (31631)

22. ((Transmis* or transmit*) adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (16998)
23. (Infectio* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (88235)
24. (Contagio* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (346)
25. (Isolation adj3 (duration* or time or length* or period*)).tw,kf. (4988)
26. (clearance* adj5 (duration* or time* or length* or period*)).tw,kf. (11671)
27. (viral load* adj5 (duration* or time* or length* or period*)).tw,kf. (3673)
28. cycl* threshold*.tw,kf. (3987)
29. CT value*.tw,kf. (9093)
30. (peak* adj1 (vir* load* or vir* concentrat*)).tw,kf. (699)
31. (exp virus load/ or exp disease transmission/) and time/ (2327)
32. exp *virus load/ or exp *disease transmission/ (50894)
33. chain of transmission.tw,kf. (522)
34. incubat*.tw,kf. (433000)
35. incubation time/ (60923)
36. time factor/ (49558)
37. time/ (331272)
38. (latent or latency).tw,kf. (250875)
39. latent virus infection/ or latent period/ (60222)
40. (time adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (110566)
41. (period adj5 (asymptom* or symptom* or onset or clinical presentation)).tw,kf. (25792)
42. (asymptom* adj5 (duration or period or length*)).tw,kf. (3234)
43. (generation adj3 time).tw,kf. (6508)
44. transmission.ti. (85460)
45. infectious.ti. (62488)
46. (shed* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (4397)
47. (case* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (142003)
48. virus shedding/ (11181)
49. (PCR positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (659)
50. (culture positiv* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (696)
51. (Viral adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (15778)
52. (Virus* adj5 (duration* or time* or length* or period* or peak*)).tw,kf. (18649)
53. serial interval*.tw,kf. (522)
54. exp asymptomatic disease/ (34329)
55. asymptomatic carrier/ (1853)
56. asymptomatic transmission/ (148)
57. or/22-56 (1693232)
58. transmiss*.tw,kf. (567326)
59. transmit*.tw,kf. (243833)
60. (breakthrough or break through).tw,kf. (45094)
61. viral load*.tw,kf. (68280)
62. viral burden.tw,kf. (1580)
63. viral level*.tw,kf. (546)

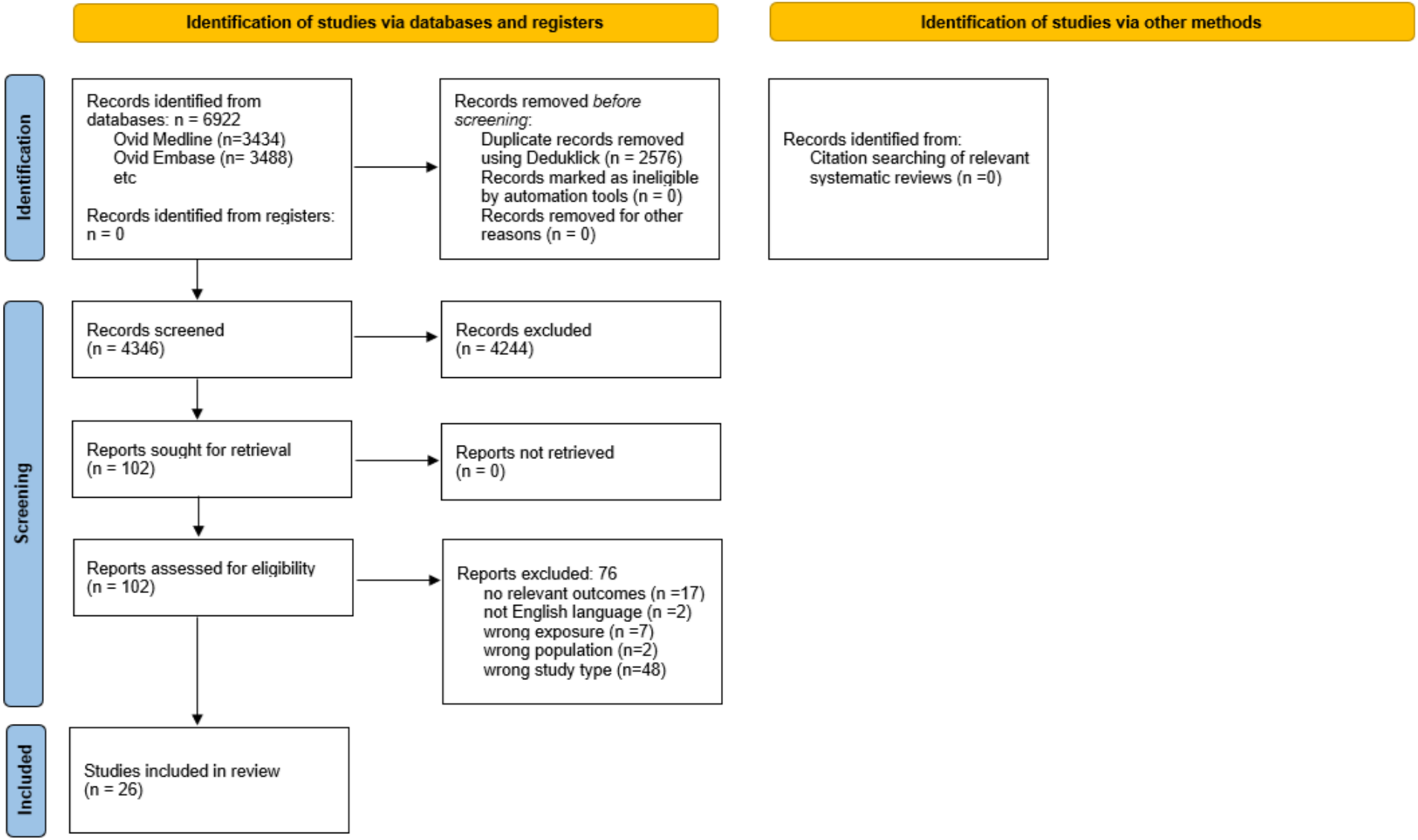
64. (shed*1 or shedding).tw,kf. (163228)
65. cytopath* effect*.tw,kf. (9960)
66. exp disease transmission/ (256059)
67. cytopathogenic effect/ (11967)
68. or/58-67 (1141760)
69. asymptomatic*.tw,kf. (292636)
70. symptomatic*.tw,kf. (365605)
71. pre-symptomatic.tw,kf. (3651)
72. non-symptomatic.tw,kf. (1729)
73. (symptom free or symptom-free).tw,kf. (13043)
74. no symptom*.tw,kf. (18759)
75. with* symptom*.tw,kf. (134836)
76. symptomless.tw,kf. (2902)
77. symptom* status.tw,kf. (2749)
78. or/69-77 (698790)
79. 68 and 78 (34598)
80. 57 or 79 (1715344)
81. 21 and 80 (4642)
82. limit 81 to yr="2009 -Current" (4293)
83. limit 81 to dc=20090101-20240731 (4335)
84. 82 or 83 (4335)
85. limit 84 to conference abstract (847)
86. 84 not 85 (3488)

Deviations

There were no deviations from the protocol.

Annexe B. Study selection flowchart

Figure B.1. PRISMA diagram



Text version of Figure B.1. PRISMA diagram

A PRISMA diagram showing the flow of studies through this review, ultimately including 26 studies.

From identification of studies via databases and registers, n=6,922 records identified from databases:

- Ovid Medline (n=3,434)
- Ovid Embase (n=3,488)

From these, records removed before screening:

- duplicate records removed using Deduklick (n=2,576)
- duplicate records removed manually (n=0)
- records marked as ineligible by automation tools (n=0)
- records removed for other reasons (n=0)

n=4346 records screened, of which n=4244 were excluded, leaving n=102 papers sought for retrieval, of which n=0 were not retrieved.

No studies were identified from identification of studies via other methods: n=0 studies were identified from expert consultation.

Of the n=102 papers assessed for eligibility, n=76 reports were excluded:

- no relevant outcomes (n=17)
- not English language (n=2)
- wrong exposure (n=7)
- wrong population (n=2)
- wrong study type (n=48)

n=26 papers included in the review.

Annexe C. Excluded full texts

Wrong study type (48 studies)

Arankalle and others. 'Role of host immune response and viral load in the differential outcome of pandemic H1N1 (2009) influenza virus infection in Indian patients' PLoS ONE [Electronic Resource] 2010: volume 5, issue 10, 1

Archer and others. 'Reproductive number and serial interval of the first wave of influenza A(H1N1)pdm09 virus in South Africa' PLoS ONE [Electronic Resource] 2012: volume 7, issue 11, e49482

Aspinall and others. 'An observational study of influenza A(H1N1)pdm09 viral shedding and resistance under standard-duration oseltamivir treatment' Southern African Journal of Epidemiology and Infection 2013: volume 28, pages 122 to 125

Beutel and others. 'Virus-associated hemophagocytic syndrome as a major contributor to death in patients with 2009 influenza A (H1N1) infection' Critical Care (London, England) 2011: volume 15, issue 2, page R80

Chen and others. 'Nosocomial Co-Transmission of Avian Influenza A(H7N9) and A(H1N1)pdm09 Viruses between 2 Patients with Hematologic Disorders' Emerging Infectious Diseases 2016: volume 22, issue 4, pages 598 to 607

Chen and others. 'Risk factors for prolonged shedding of 2009 H1N1 influenza virus' Indian Pediatrics 2011: volume 48, issue 12, pages 961 to 963

Chen and others. 'Clinical features of severe influenza A (H1N1) virus infection' Indian Journal of Pediatrics 2013: volume 80, pages 97 to 101

Cheng 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, pages 182 to 185

Chin and others. 'Viral shedding of 2009 pandemic H1N1 and evaluation of quarantine recommendations' Japanese Journal of Infectious Diseases 2012: volume 65, issue 2, pages 105 to 110

Duchamp and others. 'Pandemic A(H1N1)2009 influenza virus detection by real time RT-PCR: Is viral quantification useful?' Clinical Microbiology and Infection 2010: volume 16, pages 317 to 321

Escuret and others. 'Oseltamivir-zanamivir bitherapy compared to oseltamivir monotherapy in the treatment of pandemic 2009 influenza A(H1N1) virus infections' Antiviral Research 2012: volume 96, issue 2, pages 130 to 137

Fox and others. 'Pandemic influenza (H1N1): Impact on lung transplant recipients and candidates' Journal of Heart and Lung Transplantation 2010: volume 29, pages 1,034 to 1,038

Fraaij and others. 'Evaluation of the antiviral response to zanamivir administered intravenously for treatment of critically ill patients with pandemic influenza A (H1N1) infection' Journal of Infectious Diseases 2011: volume 204, issue 5, pages 777 to 782

Fry and others. 'Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial' The Lancet Infectious Diseases 2014: volume 14, issue 2, pages 109 to 118

Gandhoke and others. 'Pandemic Influenza A (H1N1) 2009 in India: duration of virus shedding in patients under antiviral treatment' Indian Journal of Medical Microbiology 2011: volume 29, issue 1, pages 37 to 41

Hien and others. 'Early pandemic influenza (2009 H1N1) in Ho Chi Minh city, Vietnam: A clinical virological and epidemiological analysis' PLoS Medicine 2010: volume 7, issue 5

Jackson and others. 'Viral shedding in recipients of live attenuated influenza vaccine in the 2016 to 2017 and 2017 to 2018 influenza seasons in the United Kingdom' Clinical Infectious Diseases 2020: volume 70, issue 12, pages 2,505 to 2,513

Kay and others. 'Shedding of pandemic (H1N1) 2009 virus among health care personnel, Seattle, Washington, USA' Emerging Infectious Diseases 2011: volume 17, issue 4, pages 639 to 644

Kenah. 'Contact intervals, survival analysis of epidemic data, and estimation of R(0)' Biostatistics 2011: volume 12, issue 3, pages 548 to 566

Khoury and others. 'Duration of viral shedding and factors associated with prolonged shedding among inpatients with influenza treated with oseltamivir: a prospective cohort study' European Journal of Clinical Microbiology and Infectious Diseases 2018: volume 37, issue 2, pages 319 to 323

Kropp and others. 'Pandemic (H1N1) 2009 outbreak at Canadian Forces cadet camp' Emerging Infectious Diseases 2010: volume 16, issue 12, pages 1,986 to 1,989

Lalueza and others. 'Influence of viral load in the outcome of hospitalized patients with influenza virus infection' European Journal of Clinical Microbiology and Infectious Diseases 2019: volume 38, issue 4, pages 667 to 673

Leung and others. 'Delayed oseltamivir treatment is associated with longer viral shedding of pandemic (H1N1) 2009 virus' Epidemiology and Infection 2012: volume 140, issue 5, pages 814 to 817

Li and others. 'Correlation of pandemic (H1N1) 2009 viral load with disease severity and prolonged viral shedding in children' Emerging Infectious Diseases 2010: volume 16, issue 8, pages 1,265 to 1,272

Ling and others. 'Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection' Clinical Infectious Diseases 2010: volume 50, pages 963 to 969

Lu and others. 'Relationship between respiratory viral load and lung lesion severity: A study in 24 cases of pandemic H1N1 2009 influenza A pneumonia' Journal of Thoracic Disease 2012: volume 4, pages 377 to 383

Malato and others. 'Pandemic influenza A(H1N1) 2009: molecular characterisation and duration of viral shedding in intensive care patients in Bordeaux, south-west France, May 2009 to January 2010' Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 2011: volume 16, issue 4, page 27

Na and others. 'Duration of viral shedding in patients admitted to hospital with pandemic influenza A/H1N1 2009 infection' Journal of Medical Virology 2011: volume 83, issue 1, pages 5 to 9

Ng and others. 'Benign clinical course in H1N1 2009 influenza infection in young oseltamivir-treated immunocompromised patients with kidney disease in Singapore' Pediatric Infectious Disease Journal 2013: volume 32, issue 3, pages 298 to 300

Nishiura and others. 'Estimation of the incubation period of influenza A (H1N1-2009) among imported cases: addressing censoring using outbreak data at the origin of importation' Journal of Theoretical Biology 2011: volume 272, issue 1, pages 123 to 130

Poeppl and others. 'Performance of the QuickVue Influenza A+B rapid test for pandemic H1N1 (2009) virus infection in adults' PLoS ONE [Electronic Resource] 2011: volume 6, issue 12, e28089

Poletti and others. 'The effect of risk perception on the 2009 H1N1 pandemic influenza dynamics' PLoS ONE [Electronic Resource] 2011: volume 6, issue 2, e16460

Qiu and others. 'Early adaptive humoral immune responses and virus clearance in humans recently infected with pandemic 2009 H1N1 influenza virus' PLoS ONE [Electronic Resource] 2011: volume 6, issue 8, e22603

Renaud and others. 'H275Y mutant pandemic (H1N1) 2009 virus in immunocompromised patients' Emerging Infectious Diseases 2011: volume 17, pages 653 to 660

Ryoo and others. 'Factors promoting the prolonged shedding of the pandemic (H1N1) 2009 influenza virus in patients treated with oseltamivir for 5 days' Influenza and Other Respiratory Viruses 2013: volume 7, issue 5, pages 833 to 837

Schoub. 'Pandemic influenza (H1N1) 2009 (swine flu)' South African Medical Journal 2009: volume 99, pages 576 to 577

Seville and others. '2009 H1N1 influenza in hospitalized transplant recipients' Transplantation 2010: volume 90, pages 571 to 574

Shen and others. 'Epidemiologic parameters and evaluation of control measure for 2009 novel influenza a (H1N1) in Xiamen, Fujian Province, China' Virology Journal 2012: volume 9, page 20

To and others. 'Viral load in patients infected with pandemic H1N1 2009 influenza A virus' Journal of Medical Virology 2010: volume 82, pages 1 to 7

Tom 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

Verma and others. 'Clinical profile and outcome of influenza A/H1N1 in pediatric oncology patients during the 2015 outbreak: a single center experience from Northern India' Journal of Pediatric Hematology/Oncology 2017: volume 39, pages e357 to e358

Wang and others. 'Duration of viral shedding of influenza A (H1N1) virus infection treated with oseltamivir and/or traditional Chinese medicine in China: a retrospective analysis' Journal of Traditional Chinese Medicine 2012: volume 32, issue 2, pages 148 to 155

Watson and others. 'Characterisation of a wild-type influenza (A/H1N1) virus strain as an experimental challenge agent in humans' Virology Journal 2015: volume 12, page 13

Xiao and others. 'Hospitalized patients with novel influenza A (H1N1) virus infection: Shanghai, June to July 2009' Chinese Medical Journal 2010: volume 123, pages 401 to 405

Yamagishi and others. 'Onset and duration of symptoms and timing of disease transmission of 2009 influenza A (H1N1) in an outbreak in Fukuoka, Japan, June 2009' Japanese Journal of Infectious Diseases 2010: volume 63, issue 5, pages 327 to 331

Yang and others. 'Pandemic H1N1 and seasonal H3N2 influenza infection in the human population show different distributions of viral loads, which substantially affect the performance of rapid influenza tests' Virus Research 2011: volume 155, issue 1, pages 163 to 167

Yang and others. 'Early experience of the pandemic influenza H1N1 2009 epidemic in Taiwan' Journal of the Chinese Medical Association: JCMA 2011: volume 74, issue 7, pages 298 to 304

Zhou and others. 'Clinical features of initial cases of 2009 pandemic influenza A (H1N1) in Macau, China' Chinese Medical Journal 2010: volume 123, issue 19, pages 2,651 to 2,654

Wrong population (2 studies)

Neira and others. 'Characterization of viral load, viability and persistence of influenza A virus in air and on surfaces of swine production facilities' PLoS ONE [Electronic Resource] 2016: volume 11, issue 1, e0146616

White and others. 'Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA' Influenza and other Respiratory Viruses 2009: volume 3, pages 267 to 276

Wrong exposure (7 studies)

Bai and others. 'Impact of RNA degradation on influenza diagnosis in the surveillance system' Diagnostic Microbiology and Infectious Disease 2021: volume 100, issue 4, page 115,388

Deng and others. 'Comparison of patients hospitalized with COVID-19, H7N9 and H1N1' Infectious Diseases of Poverty 2020: volume 9, issue 1, page 163

Gordon and others. 'Influenza transmission dynamics in urban households, Managua, Nicaragua, 2012 to 2014' Emerging Infectious Diseases 2018: volume 24, issue 10, pages 1,882 to 1,888

Iyengar and others. 'Case-ascertained study of household transmission of seasonal influenza - South Africa, 2013' Journal of Infection 2015: volume 71, issue 5, pages 578 to 586

Lehners and others. 'Long-term shedding of influenza virus, parainfluenza virus, respiratory syncytial virus and nosocomial epidemiology in patients with hematological disorders' PLoS ONE [Electronic Resource] 2016: volume 11, issue 2, e0148258

Rodrigues Guimaraes Alves and others. 'Influenza B viral load analysis in patients with acute respiratory infection from a tertiary hospital in Brazil' Journal of Medical Virology 2020: volume 92, issue 8, pages 1,350 to 1,354

Tsang and others. 'Influenza A virus shedding and infectivity in households' Journal of Infectious Diseases 2015: volume 212, issue 9, pages 1,420 to 1,428

Not English language (2 studies)

Duque and others. 'The early days of pandemic (H1N1) 2009 virus infection in the central region of Portugal' Revista Portuguesa de Pneumologia 2010: volume 16, issue 6, pages 870 to 879

Santa-Olalla Peralta and others. '[Enhanced surveillance of initial cases of pandemic influenza (H1N1) 2009 infection in Spain, April to June 2009]' Revista Espanola de Salud Publica 2010: volume 84, issue 5, pages 529 to 546

No relevant outcomes (17 studies)

Asiedu-Bekoe and others. 'Mass oseltamivir prophylaxis halts pandemic influenza A H1N1 2009 outbreak in a secondary school in Ashanti Region, Ghana' Ghana Medical Journal 2012: volume 46, issue 4, pages 219 to 224

Baccin and others. 'Epidemiological profile of influenza a cases in southern Brazil in the post-pandemic period' Journal of Antivirals and Antiretrovirals 2013: volume 5, pages 145 to 150

Baker and others. 'Transmission of pandemic A/H1N1 2009 influenza on passenger aircraft: retrospective cohort study' 2010: volume 1, page c2424

de Serres and others. 'Contagious period for pandemic (H1N1) 2009' Emerging Infectious Diseases 2010: volume 16, pages 783 to 788

Friesema and others. 'Course of pandemic influenza A(H1N1) 2009 virus infection in Dutch patients' Influenza and other Respiratory Viruses 2012

Harwood and others. 'Two aircraft carriers' perspectives: a comparative of control measures in shipboard H1N1 outbreaks' Disaster Medicine and Public Health Preparedness 2013: volume 7, issue 1, pages 29 to 35

Lee and others. 'Comparison of pandemic (H1N1) 2009 and seasonal influenza viral loads, Singapore' Emerging Infectious Diseases 2011: volume 17, issue 2, pages 287 to 291

Lee and others. 'Viral clearance and inflammatory response patterns in adults hospitalized for pandemic 2009 influenza A(H1N1) virus pneumonia' Antiviral Therapy 2011: volume 16, issue 2, pages 237 to 247

Liu and others. '2009 pandemic characteristics and controlling experiences of influenza H1N1 virus 1 year after the inception in Hangzhou, China' Journal of Medical Virology 2010: volume 82, issue 12, pages 1,985 to 1,995

Liu and others. 'The Effectiveness of Age-Specific Isolation Policies on Epidemics of Influenza A (H1N1) in a Large City in Central South China' PLoS ONE [Electronic Resource] 2015: volume 10, issue 7, e0132588

Pamaran and others. 'Epidemiological characterization of influenza A(H1N1)pdm09 cases from 2009 to 2010 in Baguio City, the Philippines' PLoS ONE [Electronic Resource] 2013: volume 8, issue 11, e79916

Pronier and others. 'Respiratory Influenza viral load as a marker of poor prognosis in patients with severe symptoms' Journal of Clinical Virology 2021: volume 136

Redlberger-Fritz and others. 'Distinct differences in clinical manifestation and viral laboratory parameters between children and adults with influenza A(H1N1)pdm09 infection: a retrospective comparative analysis' Journal of Medical Virology 2014: volume 86, issue 6, pages 1,048 to 1,055

To and others. 'Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection' Clinical Infectious Diseases 2010: volume 50, pages 850 to 859

Unal and others. 'Molecular epidemiology and disease severity of influenza virus infection in patients with haematological disorders' Journal of Medical Virology 2023: volume 95

Wenger and others. '2009 Pandemic influenza A H1N1 in Alaska: temporal and geographic characteristics of spread and increased risk of hospitalization among Alaska Native and Asian/Pacific Islander people' Clinical Infectious Diseases 2011: volume 52, pages S189 to S197

Zhang and others. 'Epidemiological and clinical features of 308 hospitalized patients with novel 2009 influenza A (H1N1) virus infection in China during the first pandemic wave' Intervirology 2011: volume 54, issue 3, pages 164 to 170

Annexe D. Data extraction tables

CI = confidence interval, IQR = interquartile range, PCR = polymerase chain reaction, RNA = ribonucleotide acid, RT-PCR = reverse transcription polymerase chain reaction, SD = standard deviation

Study	Country, time period	Study type	Population	Outcome type	Outcomes
Bhattarai 2011 (4)	USA, 2009	Prospective cohort Telephone survey. Response rate not reported Non-probability sampling (exact method unclear)	26 participants identified by telephone survey during an elementary school outbreak Median age: 8 years old, range: 2 to 45 years old, 85% 2 to 14 years old 16 male, 10 female 3 out of 26 participants took oseltamivir	Time to viral clearance	Median duration of H1N1pdm09 detection using RT-PCR: 6 days (range: 1 to 13 days) Difference in viral shedding duration by RT-PCR between younger children and adults was not statistically different (test for trend across ordered age groups, p=0.6; K-sample test on the equality of medians, p=0.3) Difference in viral shedding duration by culture between different age groups was not statistically different (test for trend across ordered age groups, p=0.8; K-sample test on the equality of medians, p=0.4) The median duration of shedding by RT-PCR among 3 participants taking oseltamivir was 7 days (range: 3 to 10 days). The 23 persons who reported not taking any oseltamivir median duration of shedding was 6 days (range: 1 to 13 days, K-sample test on the equality of medians, p= 0.3).
				Location of exposure	Exposure occurred at an elementary school, subsequent contacts found via telephone survey
Esposito 2011 (1)	Italy, 2009	Prospective cohort Non-probability sampling (exact method unclear)	74 children with H1N1pdm09, presenting to hospital with influenza like symptoms 36 males, 38 females. Mean age 5.2 years SD: 4.9 years. No comorbidities but 44 were hospitalised because of pneumonia. Those needing antiviral treatment were excluded from study.	Viral load over time, Time to viral clearance	Mean viral load (log_{10} copies per millilitre including ±SD) and number of children shedding virus from days 1 to 17 Day 1 to 2: mean viral load was 8.19 (±1.41); children shedding virus was 74/74 Day 3: mean viral load was 7.30 (±1.48); children shedding virus was 74/74day 5: mean viral load was 7.00 (±1.23); children shedding virus was 57/74 Day 7: mean viral load was 3.90 (±2.83); children shedding virus was 42/74 Day 9: mean viral load was 2.12 (±3.05); children shedding virus was 35/74 Day 11: mean viral load was 1.09 (±2.32); children shedding virus was 16/74 Day 13: mean viral load was 1.00 (±1.66); children shedding virus was 14/74 Day 15: mean viral load was 0.87 (±2.47); children shedding virus was 10/74 Day 17: mean viral load was 0; children shedding virus was 0/74 Viral load was not associated with patient age

Study	Country, time period	Study type	Population	Outcome type	Outcomes
					Viral load was not associated with risk of developing pneumonia because the percentage of children who shed the virus for more than 9 days and were admitted to hospital for pneumonia was similar (68.5% versus 51.2% p>0.05) Households with children with prolonged shedding (≥9 days) had significantly more influenza like infections during the 2 weeks after the onset of initial disease, when compared to children who shed virus for less than 9 days (72.3% vs 41.4%; p<0.05)
Fraaij 2015 (2)	France and Netherlands, 2011 to 2012 and 2012 to 2013 influenza seasons	Prospective cohort Non-probability sampling (exact method unclear) Participants were enrolled from 8 hospital centres from across France and the Netherlands	15 immunocompromised patients positive for H1N1pdm09 Median age 52 (range 2 to 62 years old) 10 males, 5 females 13 taking antiviral therapy	Time to viral clearance	Detection of viral RNA by RT-PCR from day 3 onwards in patients who were influenza-positive at baseline. Day 3: 11/15 influenza positive, 4/15 influenza not detected Day 6: 5/10 influenza positive, 3/10 influenza not detected, 2/10 not tested Day 9: 4/7 influenza positive, 1/7 influenza not detected,2/7 not tested Day 12: 1/4 influenza positive, 2/4 influenza not detected, 1/4 not tested Day 15: 1/3 influenza positive, 2/3 not tested
Giannella 2011 (11)	Spain, 2009	Prospective cohort 64 participants were enrolled from one large tertiary teaching hospital, only 58 had extractable median viral load data Non-probability sampling (exact method unclear)	64 participants positive for H1N1pdm09, who were hospitalised for at least 48 hours 27 males, 37 females Mean age reported as those with prolonged viral shedding 47.6 years old (SD: 17.5) and those without prolonged viral shedding 43.9 years old (SD: 13) Comorbidities included intensive care unit admission, immunocompromised, those with chronic comorbidity Prolonged viral shedding was defined as the detection of H1N1 virus by RT-PCR on day 7 after diagnosis All patients treated with oseltamivir	Viral load over time	Persistence of viral shedding (positive 7 days after diagnosis): found in 16 of the 64 patients, of whom 6 continued to test positive on day 14 after the initial positive sample Median relative viral load for patients with specimens analysed on the days listed from diagnosis: Day 0: 0.1 (IQR 0.02 to 2.0), 58 patients Day 2 to 4: 0.02 (IQR 0.002 to 0.1), 15 patients Day 5 to 7: 0.02 (IQR 0.004 to 0.02), 15 patients Day 8 to 10: 0.01 (IQR 0.002 to 0.17), 10 patients Day 11 to 13: 0.003, 1 patient Day 14 to 16: 0.0003, 1 patient

Study	Country, time period	Study type	Population	Outcome type	Outcomes
Gorini da Veiga 2012 (5)	Brazil, 2009	Cross-sectional Non-probability sampling (exact method unclear) Participants were selected from all patients presenting with acute respiratory infection in health units throughout Rio Grande do Sul state, Brazil	198 patients positive for H1N1pm09, sampled when attending any health unit across Rio Grande do Sul state 56.4% female, 43.6% male Age range from 0 to 70 years old	Viral load over time	Median viral load on day 0 to day 5 or later after onset of symptoms for 198 participants (IQR) less than 1 day: 7.3 (0.2 to 180.1) 1 day: 14.3 (0.6 to 161.2) 2 days: 20.32 (2.3 to 222.1) 3 days: 3.1 (0.1 to 43.5) 4 days: 2.0 (0.04 to 12.0) 5 days or more 0.6 (0.1 to 14.6)
Ip 2015 (20)	Hong Kong, 2008 to 2014	Prospective cohort Non-probability sampling (exact method unclear) Participants were secondary cases, recruited during a community randomised controlled trial and observational study	33 secondary cases based within the community who tested positive for H1N1pdm09 9 males, 24 females Number of participants per age category: 0 to 15 year olds: 7 16 to 30 year olds: 4 31 to 45 year olds: 17 Over 45 year olds: 5 Number on antiviral treatment not clearly reported instead reference to "very few cases were prescribed antivirals for illness"	Viral load over time	Geometric mean of viral load (mean log_{10} copies per millilitre) according to time in relation to acute respiratory illness onset 1 or 2 days before: 2.7 Day 0: 4.3 Day 1 or 2: 4.5
				Location of exposure	In the community within households
Janjua 2012 (6)	Canada, 2009	Cross-sectional Telephone survey contacting households with a child enrolled at a local school Response rate was not reported Non-probability sampling (exact method unclear)	408 participants, 253 from the school and 191 from an aboriginal reserve. Cases tested for antibody response to H1N1pdm09 Median age of 15 (range 1 to 86 years old) 217 females, 186 males	Serial interval	Using both index and secondary case pairs serial interval was 3.4 days (95% CI 2.1 to 5.13) Using lab confirmed index cases, the median serial interval was 4.21 days (CI 1.6 to 9.78)
				Location of exposure	Elementary school and aboriginal reserve

Study	Country, time period	Study type	Population	Outcome type	Outcomes
			40 with chronic conditions 90 vaccinated 2008 to 2009 influenza season, 100 for 2007 to 2008 influenza season, 209 of the participants were aboriginal No one was prescribed antiviral medication or hospitalised		
Jia 2011 (7)	China, September 2009 to January 2010	Prospective cohort Non-probability sampling (exact method unclear). Participants were taken from outpatients tested for influenza	67 outpatients with influenza-like illness who presented to the hospital within 3 days of symptoms and were subsequently diagnosed with H1N1pdm09 19 males and 48 females, median age 23.7 years (range 17 to 34) Study authors excluded patients with obesity, comorbidity diseases or who received antiviral therapy	Time to viral clearance	Number of H1N1pdm09 patients shedding virus from disease onset Day 2: 67/67 Day 3: 67/67 Day 4: 55/67 Day 5: 49/67 Day 6: 37/67 Day 7: 32/67 Day 8: 21/67 Day 9: 10/67 Day 10: 1/67 Day 11: 0/67 No cases were positive by 11 days after disease onset The median interval between symptom onset and undetectable test result was 6 days (range 4 to 10 days)
Killingley 2010 (8)	UK, September 2009 to January 2010	Prospective cohort Non-probability sampling (exact method unclear) Subjects recruited from the hospital and community if presented with influenza-like symptoms and had not experienced illness for more than 48hours or been in hospital for more than 96 hours	19 participants, 11 from hospitals and 8 from the community, with H1N1pdm09 Median age 12, age range 0 to 34 years old 9 males, 10 females 11 were taking antiviral therapy	Time to viral clearance	When detected by PCR the median duration of viral shedding was 6.2 days (range 3 to 10 days) No difference between adults (6.1 days) and children (6.3 days, p=0.89) Duration of shedding for hospital cases (mean 6.8 days) was slightly longer than that of community cases (mean 5.7 days, this was not significant
				Culture positivity over time	12/19 were positive for H1N1pdm09 on culture on day 1 Mean duration of viral shedding by culture for these 12 cases was 4.7 days (range 3 to 8 days)

Study	Country, time period	Study type	Population	Outcome type	Outcomes
					Calculation was repeated with the assumption that 6 negative cases shed no virus making duration = 0 days. Mean duration was then 2.9 days (range 0 to 8 days). Median duration was 3 days 6/19 subjects shed virus for at least 5 days from onset of illness
Killingley 2016 (9)	UK, September 2009 to January 2010	Prospective cohort Non-probability sampling (exact method unclear)	42 patients with H1N1pdm09 from hospitals (18) and the community (24) 15 children, 27 adults 20 of 42 received antiviral treatment (48%) 39 patients with H1N1pdm09 from hospitals for whom culture results were obtained Sex and age breakdown not reported	Time to viral clearance	Median duration of viral shedding (measured by PCR): 6.2 days from symptom onset (range: 2 to 15 days, IQR: 5 to 7 days) No significant difference was found between adults and children (mean difference: 0.29 days, 95% CI: -1.33 to 1.90 days, p=0.720)
				Culture positivity over time	Mean duration of culture positivity: 4.6 days (range 3 to 10 days, IQR 4 to 5 days) 10 of 39 patients shed live virus for at least 5 days from onset of illness
Lessler 2009 (10)	USA, April 2009	Cross-sectional 2 online surveys were administered to 2,934 students and employees in the school, recruited by mass email message to all students, parents, and employees. Non probabilistic sampling Response rate was 83% (2,225 of 2,686), and 92% of employees (228 of 248) Of those who underwent lab testing 124 were positive for H1N1pdm09, 119 received a telephone interview Additionally, of the 124 positive for H1N1pdm09, 119 received a telephone interview	124 students (120) or employees (4) of a high school with lab confirmed H1N1pmd09 Median age amongst students: 16 years (range: 14 to 19 years), 61% female Median age amongst employees: 25 years (range: 20 to 47 years), 75% female	Incubation period	Median incubation period: 1.4 days (95% CI: 1.0 to 1.8 days). Estimated by identifying earliest and latest possible dates of exposure and the date of onset of symptoms), log-normal distribution fit to the resulting data. Number of cases included in the analysis unclear Symptoms developed in 95% of the cases by 2.2 days (95% CI: 1.7 to 2.6 days)
				Serial interval	Serial interval of 2.7 days (95% CI: 2.0 to 3.5 days). Estimated from data from index and secondary case pairs where a single likely index case could be identified and symptom onset date known for index and secondary case. Number of cases included in the analysis unclear Serial interval was less than 5.1 days (95% CI: 3.6 to 6.5 days) in 95% of cases Note: authors reported the outcome as generation time, however as it relied on patient-reported symptom or disease onset we have redefined as serial interval
				Location of exposure	Presumed to be the high school. 14 of the students reported a recent travel history to Mexico

Study	Country, time period	Study type	Population	Outcome type	Outcomes
Li 2010 (3)	China, May 2009 to February 2010	Prospective cohort Sampling method unclear	15 chronic haemodialysis patients Mean age: 47.6 years (SD: 22.0 years) 9 male, 6 female All received oseltamivir	Incubation period	Median incubation period: 4 days (range: 1 to 7 days)
				Time to viral clearance	Median duration of positive RT-PCR: 12 days (range: 7 to 19 days)
Loeb 2012 (14)	Canada, November to December 2009	Prospective cohort 10 Hutterite colonies were enrolled, selected based on convenient location for access by research nurses Non-probability sampling Standardised checklist of self-reported symptoms Response rate not reported	97 cases in Hutterite communities (isolated, communal farming) Demographics not reported for the H1N1pdm09 subgroup	Time to viral clearance	Mean duration of viral shedding all H1N1pdm09 cases: 4.8 days (SD: 2.9 days, range 1 to 15 days) Mean duration of viral shedding asymptomatic H1N1pdm09 cases: 3.2 days (SD: 2.2 days) Asymptomatic shedding was observed over an 8 day period (presumed to be the upper bound of the range of asymptomatic viral shedding)
				Viral load over time	Viral load peaked at or before onset of acute respiratory illness, then declined gradually for 6 to 8 days, with ongoing shedding until 12 to 14 days after acute respiratory illness
Meschi 2011 (12)	Italy, April to December 2009	Retrospective cohort Sampling method unclear but likely non-probability (cases at the National Institute for Infectious Diseases)	39 hospitalised cases for whom serial nasopharyngeal samples were available, n=11 with H1N1pdm09 and pneumonia, n=28 with H1N1pdm09 without pneumonia For those with pneumonia: Median age was 51 years (IQR 41 to 63.5 years)4 males and 7 females 90.9% received antiviral therapy For those without pneumonia: Median age was 26 years (IQR 18.5 to 35.5) 19 males, 9 females	Time to viral clearance	Mean duration of positive nasopharyngeal PCR results from symptom onset in n=11 patients with H1N1pdm09 and pneumonia: 15.4 days (SD: 9.0 days) Mean duration of positive nasopharyngeal PCR results from symptom onset in n=28 patients with H1N1pdm09 without pneumonia: 7.5 days (SD: 3.4 days)

Study	Country, time period	Study type	Population	Outcome type	Outcomes
			67.9% received antiviral therapy		
Petrie 2013 (15)	USA, 2010 to 2011	Prospective cohort Households targeted for enrolment based on selected primary healthcare providers within the local health system, and contacted by direct mail Not explicit, but likely non-probability sampling Response rate not reported	26 cases of H1N1pdm09 (amongst 1,441 participants in 328 households) Demographics for the H1N1pdm09 subgroup not reported	Serial interval	Mean serial interval (days between onset of symptoms index cases to onset of symptoms in transmission linked secondary cases): 2.8 days (95% CI 1.3 to 5.0 days) Of note, there were only 5 secondary H1N1pdm09 cases
				Location of exposure	Household transmission (for 5 transmission pairs)
Rodrigues Guimaraes Alves 2020 (18)	Brazil, 2009 to 2013	Cross-sectional Sampling: patients attending a tertiary hospital in Brazil, non-probability sampling	162 cases with H1N1pdm09 (n=15 asymptomatic, n=76 hospitalised, n=71 symptomatic outpatients) Median age: 12.5 years (SD: 20.54 years, range 0.08 to 77 years)	Viral load over time	Amongst 71 symptomatic outpatients: n=28 patients where viral load was measured one to 2 days after symptom onset. Mean viral load: 7.07 log_{10} RNA copies per millilitre (SD: 1.54) n=33 patients where viral load measured 3 to 4 days after symptom onset. Mean viral load: 5.97 log_{10} RNA copies per millilitre (SD: 1.86) n=10 patients where viral load measured 5 to 8 days after symptom onset. Mean viral load: 6.43 log_{10} RNA copies per millilitre (SD: 2.48) Higher mean viral load within 2 days of disease onset compared to 3 to 4 days of disease onset (p=0.016)
Roll 2011 (21)	Israel, April to July 2009	Retrospective cohort Sampling: database of all cases with confirmed swine flu at the National Influenza Center. Non-probability sampling	Within the infection network there were 183 'nodes' representing cases, and 123 links between them. However, 55.2% of the 'nodes' had no outgoing link Total number of index case and secondary case pairs in the analysis unclear	Serial interval	Serial interval: 2.92 days (SD: 1.79 days) based on a generation time distribution of up to 7 days Note: authors reported the outcome as generation time, however as it relied on patient-reported symptom or disease onset we have redefined as serial interval
Roosenhoff 2020 (26)	Europe, USA, China (Hong Kong),	Prospective cohort	683 participants All aged under 13	Time to viral clearance	Median time to virus RNA clearance was longest for young children (under 5 years, n=320, median range 9.9 to 11.5) compared with older children (over 5, n=363, median range 7.2 to 9.0 days)

Study	Country, time period	Study type	Population	Outcome type	Outcomes
	Australia, South Africa, 2008 to 2015	Part of a multicentre nonrandomised longitudinal study Non purposive sampling (exact method unclear)	375 received antiviral treatment No other demographics provided		Median time to viral clearance: n=4 aged under 6 months: 11.5 days (95% CI: not reported) n=7 aged 6 months to 1 year: 10.9 days (95% CI: 6.9 to 11.8 days) n=151 aged 1 to 3 years: 9.9 days (95% CI: 9.0 to 10.2 days) n=158 aged 3 to 5 years: 10.2 days (8.9 to 10.5 days) n=270 aged 5 to 10 years: 9.0 days (8.0 to 9.7 days) n=93 aged 10 to 13 years: 7.2 days (6.8 to 8.6 days)
Suess 2012 (13)	Germany, 2007 to 2011	Prospective cohort Recruitment was embedded in a cluster randomised trial Non purposive sampling (exact method unclear)	98 participants (70 of which were index cases, 28 household contacts) Median age of index cases was 8 years old with an interquartile range between 5 to 10 94% of the index cases were under 14 57% of index cases were male 1% was vaccinated 34% received antiviral therapy	Serial interval	Serial interval was 2.4 days ± 1.5 (based on 19 cases)
Tuite 2010 (16)	Canada, 2009	Retrospective cohort Looking at medical records of Hutterite communities Non-probability sampling (exact method unclear)	3,152 participants Mean age was 21.9 years SD 15.7 Due to missing data only data from 316 participants was used to measure incubation period No other demographics provided	Incubation period	Mean incubation was 4.3 days (95% CI 2.6 to 6.6 days)
Uchida 2013 (22)	Japan, 2009 to 2010	Prospective cohort Study looking into natural history of university students with H1N1pdm09	324 participants 208 males, 116 females No other demographics provided	Incubation period	Median time from infection to fever development was 2 days (range 0 to 8 days)
				Location of exposure	Exposure occurred at a university

Study	Country, time period	Study type	Population	Outcome type	Outcomes
		Non-probability sampling (students contact designated phone number to report H1N1pdm09)			
Waiboci 2011 (19)	Kenya, 2009	Prospective cohort Non-probability sampling of participants who presented to a field clinic	106 participants (of which consented, 85 completed the study and 140 initially tested positive for H1N1pdm09) Median age was 6 years (range 4 months to 41 years) 46 males, 60 females2 participants received oseltamivir Other demographics were not provided	Culture positivity over time	Of RT-PCR-positive specimens taken on day 0 to 3 after illness onset, 81/85 (95%) were culture-positive, as were 37/40 (93%) taken on day 4 to 7, 11/20 (55%) taken on day 8 to 10, and 3/17 (18%) taken 11 days or more after illness onset
				Time to viral clearance	The median number of days H1N1pdm09 virus RNA was detectable in patients specimens was 8 days (95% CI: 7 to 10 days) after symptom onset. In majority of patients (58%) virus RNA was detected for 7 days or more, and 16% of patients 14 days or more
Wang 2012 (23)	China, 2009	Retrospective cohort Includes telephone questionnaire of students and staff at a middle school, response rate was 93.48% of the students (2,586/2,768) and 85.87% of the employees (158/184) Non-probability sampling	79 participants, mixture of staff and students Age distribution of confirmed cases was between 11 months and 59 years Other demographics not provided	Incubation period	Mean incubation period was 1.6 days (95% CI 1.2 to 2.3). The shortest and longest incubation periods among the confirmed cases were 0.4 and 4.2 days
				Location of exposure	Exposure occurred at a middle school
Wang 2017 (17)	Canada, 2007 to 2010	Prospective cohort Conducted in Hutterite communities Method of sampling unclear	97 participants with H1N1pdm09 from Hutterite communities (isolated, communal farming) 12 of 97 were asymptomatic 25% over 16 44% male 5% with more than 1 comorbidity 60% vaccinated 12% asymptomatic	Time to viral clearance	Mean viral shedding duration (±SD) among symptomatic cases was longer than in asymptomatic cases (4.97±2.93 vs 3.16 ± 2.12 days, P=.02) Being symptomatic (HR, 0.24; 95% CI, 0.10 to 0.58; P<.01) was associated with prolonged viral shedding duration 5 symptomatic cases had pre-symptomatic shedding, with shedding start date distributed as 1(20%), 3(40%), 4(20%), 5(20%) days before symptom onset

Study	Country, time period	Study type	Population	Outcome type	Outcomes
Wu 2012 (24)	Taiwan, 2009 to 2010	Prospective cohort Samples taken from a hospital population. Non-probability sampling (exact method unclear)	64 participants Recruited from one Taiwan hospital, 18 of which were categorised as 'complicated' as they were hospitalised owing to complications including pneumonia, or requiring mechanical ventilation Uncomplicated group: mean age was 26.8 ± 10.2 18 males, 28 females Complicated group: Mean age was 42.0 ± 17.7 12 males, 6 females All participants received treatment Other demographics not provided	Time to viral clearance	Mean initial viral load of the uncomplicated group was higher than the complicated group (3.4 ± 1.6 log_{10} copies/microlitre versus 1.9 ± 1.7, p =0.02) Though not statistically significant, viral loads were higher in the uncomplicated group for the first 3 days, and peak viral shedding occurred within 2 days of symptom onset in both groups There was a slower decline of viral shedding in the complicated group, but those in the uncomplicated groups all had undetectable viral RNA by day 7 after onset of symptoms
Yan 2012 (25)	China, 2009	Prospective cohort Includes online questionnaire, response rate not reported Non-probability sampling (exact method unclear)	170 participants100 from middle school aged between 11 to 15 years old 70 primary school aged between 6 to 15 years old Other demographics not provided	Time to viral clearance	Initial viral shedding was detected 2 days before symptom onset and the majority of shedding occurred 0 to 5 days after the onset of symptoms Peak virus shedding happened on the day of the onset of symptoms (maximum ratio = 230.7), followed by a steady decrease over the following 8 days (p = 0.026, R2= 0.18)
				Location of exposure	Exposure occurred in a primary school and middle school

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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 health secure.

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