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What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of RSV [respiratory syncytial virus]?

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on behalf of UNCOVER Applied Evidence Synthesis

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Declarations

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Authorship Contributions

AGW, TH, PK, DK, MD, EM, RM, ET contributed to the protocol and review design. MD designed and carried out the searches, with input from RM, ET and EM. AGW, TH, PK, DK and EM conducted title & abstract and full-text screening, data extraction and quality assessment. EM led the data synthesis and write-up, with input from AGW, TH, PK, DK, RM and ET.

Competing Interests

None to declare.

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About UNCOVER

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

What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of RSV [respiratory syncytial virus]?

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ABSTRACT

Background
This review aims to provide an evidence base on key transmission parameters for respiratory syncytial virus (RSV), to inform the assumptions that decision-makers may use in planning for and managing outbreaks of the disease.

Ten parameters of interest are considered: attack rate; secondary attack rate; basic reproduction number (R_0); generation time; incubation period; latency period; shedding rate; duration of infectiousness; doubling time; and mode of transmission.

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

Results
3,292 articles were found. After screening, 31 studies were eligible for inclusion.

Four studies examined the **attack rate** of RSV. For infants in the first year of life, this ranged from 29.4% to 68.8%; with a pattern of gradually decreasing attack rates with increasing age. One study examined the **secondary attack rate**, estimating this at 27% for all ages.

Four studies estimated **R_0**, with estimates ranging from 0.92 (95% CI 0.92-1.0) to 3.0 (range 1.5-4.0).

One study calculated the **serial interval** of RSV as 3.2 days (95% CI 2.5-4.1 days).

12 studies investigated the **duration of viral shedding**, with one study calculating an average duration of shedding among all age groups of 11.2 days (95% CI 10.1-12.3 days). Symptomatic individuals were found to shed for longer than asymptomatic; and longer shedding durations were found among infants under 1 year old, adults over 40, and immunocompromised adults (specifically transplant recipients).

Two studies investigated the **volume of RSV shed**, finding this to be higher among infants under 1 year old, adults over 40, symptomatic individuals, and people with RSV-A and RSV-B coinfections.

13 studies investigated different **routes of RSV transmission**. Mode of transmission was typically inferred rather than directly measured. Some evidence was found to suggest that fomite and

aerosol transmission routes may contribute to the spread of RSV, in addition to direct contact, but findings were inconclusive and more research is needed in this area.

The quality of the evidence was variable, with higher quality evidence found in respect of viral shedding and R_0 than in respect of other parameters of interest, overall. No primary studies were found in respect of four parameters of interest (incubation period, latency period, duration of infectiousness, and doubling time).

Discussion
The aim of this rapid review was to synthesise evidence on ten different epidemiological parameters in respect of RSV, in order to inform planning for future outbreaks of the disease. In practice, the information we found about these parameters was limited and of variable quality, but may provide an initial evidence base to inform planning assumptions and best practice guidance. More high-quality research is needed for all the parameters of interest, in order to expand and update the evidence base, for both hospital and community settings, and among all age groups.

BACKGROUND

Context

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

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

This review was conducted in order to provide an evidence base on key transmission parameters for respiratory syncytial virus (RSV). In defining parameters of interest, we were guided by those used as planning assumptions for influenza in the World Health Organization's (2017) Pandemic Influenza Risk Management guidelines, with a view to generating evidence that would allow a comparable set of assumptions to be developed for RSV.

Scope

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

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

METHODS

Protocol

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

Search Strategy

We developed a search strategy by combining search terms related to RSV and disease transmission, with no date limits. We carried out searches in three databases: Ovid MEDLINE, Embase and Global Health (CABI). The draft search strategy was adapted to and piloted in each database, and searches finalised following feedback from the review team [MD]. Search histories for each database are included as **Appendix 2**.

Screening and Selection of Studies

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

We carried out title & abstract screening and full-text screening within Covidence. Each record was independently screened by two reviewers [AGW, TH, PK, DK, EM] against the inclusion and exclusion criteria set out in **Table 1.**

	Include	**Exclude**
Population	Any (human)	Animal studies
Exposure	RSV (lab-confirmed)	ILI or SARI Bronchiolitis (in the absence of lab-confirmed RSV) Any other virus / condition
Comparator	N/A	N/A
Outcome	• Attack rate(s) • Generation interval(s) • Latent period • Incubation period • Duration of infectiousness • Reproduction number • Doubling time / growth rate • Mode(s) of transmission	• Symptomatology • Risk factors for transmission • % symptomatic • Zoonotic transmission
Study types	Observational epidemiological studies RCTs and quasi-experimental studies	Case series & case reports Animal studies In-vitro studies Modelling studies Papers with no data (commentaries, etc)
Language	English	Languages other than English
Setting	Any	--
Geographical location	Any	--
Timeframe	Any	--

Table 1. Inclusion and Exclusion Criteria for the Review

Data Extraction and Management

We created a data extraction form in Microsoft Excel and piloted it on a small number of randomly chosen studies. Data extraction was carried out by one reviewer [AGW, TH, PK, DK, EM].

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

Quality and Risk of Bias Assessment

In order to appraise the quality of included studies, we used the Joanna Briggs Institute [JBI] checklists for cross-sectional studies, cohort studies, prevalence studies and case-control studies.

Around a third of included papers did not use traditional epidemiological study designs, and lacked a suitable JBI checklist for quality appraisal. For studies using experimental designs, we used a non-validated checklist designed by UNCOVER for a previous review of SARS-CoV-2 transmission (Anderson et al., 2020). For studies using a combination of real-world data and statistical modelling to estimate R_0, we adapted the CHARMS checklist for systematic reviews of clinical prediction modelling studies (Moons et al., 2014), in order to undertake an approximate quality appraisal of these papers. Both non-JBI checklists are included in **Appendix 3**. Quality assessment was carried out by one reviewer [EM], and a 50% sample were peer-reviewed by a second reviewer [PK].

Data Synthesis

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

RESULTS

The literature databases search retrieved 3,292 articles. After screening, 31 studies were eligible for inclusion. The stages of our screening process are set out in the PRISMA diagram in **Figure 1** below.

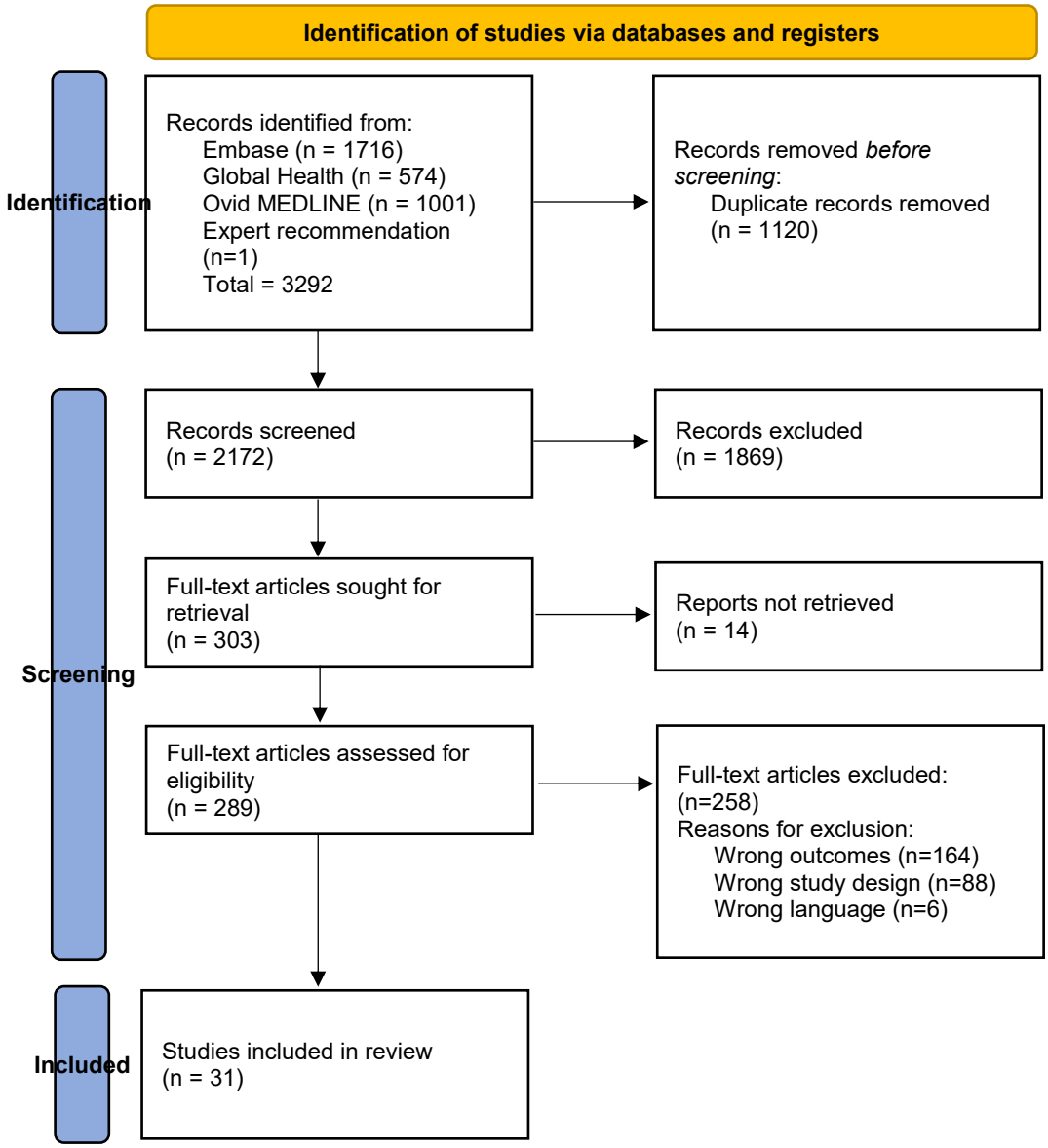

Figure 1. PRISMA flow diagram

Of the 31 included studies, 4 reported data on RSV attack rate; 1 on the secondary attack rate; 4 on the basic reproduction number; 1 on the serial interval; 12 on viral shedding; and 13 on mode of transmission (some included studies addressed more than one parameter of interest).

We found no studies measuring or calculating the incubation or latency periods, doubling time, or duration of infectiousness for RSV.

Attack rate

Attack rate is defined as "the proportion of a group that experiences the outcome under study over a given period (e.g. the period of an epidemic)" with the caveat that "because its time dimension is uncertain or arbitrarily decided, it should probably not be described as a rate" (Porta, 2014). We found four studies which aimed to calculate the attack rate of RSV.

Three studies took place in **community settings**. Hall et al. (1976) studied RSV transmission among 36 families with children (178 household members) in the US. They found an overall crude attack rate of **21.9%** among all age groups. The attack rate was highest in infants under 1 year old (**29.4%**) and lowest in adults over 17 years (**16.8%**).

The same pattern of declining crude attack rates with age was found by Munywoki et al. (2018), who carried out active surveillance of 47 households (483 household members) in Kenya over a six-month period during an RSV season: an attack rate of **56.4%** for infants under 1 year old, decreasing to **23.4%** for people aged 15-39, and **19.0%** for adults aged 40 and above.

Glezen et al. (1986) followed up 125 infants from birth, as part of the Houston Family Study in the USA. This study found an attack rate of **68.8%** among infants in the first year of life (0-12 months) and **82.6%** in the second year (13-24 months). RSV was detected via cell culture of nasal washes taken on a weekly basis during the respiratory disease season.

One study (Silva et al., 2020) took place in a **healthcare setting** – a neonatal intensive care unit [NICU] in Brazil. This study was an outbreak investigation, so may differ meaningfully from studies of RSV transmission in the community, in terms of attack rate and generation time. The study identified two separate RSV outbreaks:

- In May 2013, 10 out of 17 infants in NICU at the time were infected with RSV-A type ON-1 (an attack rate of **58.8%**).
- In a separate outbreak in June 2013, 14 infants were infected with RSV-A type NA-2 (an attack rate of **63.6%**).

In both cases, samples from all infants in NICU were tested via RRT-PCR following identification of an index case, and followed up weekly until a negative result was achieved. Molecular analysis was performed to identify the RSV genotype in each case.

Quality and Generalisability of the Evidence

This is a very limited evidence base for the attack rate of RSV, in terms of settings (three community-based, one NICU) and geographical spread. Studies consistently found the highest attack rates among the youngest children, although there was significant variation in those rates. Study quality was variable.

Notably, Munywoki et al. (2018) provided high-quality evidence from a well-designed study among all age groups. This study took place in a rural, low-income community setting, potentially limiting its generalisability to high-income or urban settings; but highly relevant from a global perspective, given estimates that ten times as many RSV infections take place among children under four in low- and middle-income countries compared to high-income countries (Shi et al., 2017).

Secondary attack rate

The secondary attack rate is defined as the “number of cases of an infection that occur among contacts within the incubation period following exposure to a primary case in relation to the total number of exposed contacts” (Porta, 2014).

One study (Hall et al., 1976) calculated the secondary attack rate among households with an index case of RSV as **27.0%** among all age groups. The reported secondary attack rate among infants under 1 year old was 45.4%. This was a very small sample of 11 infants, but appears consistent with the increase in the overall RSV attack rate among younger children.

Quality and Generalisability of the Evidence

Few conclusions can be drawn from a single study. The number of exposed household members was relatively small (63 in total). No assumptions were made for the incubation period of RSV, and (given that the study took place almost 50 years ago) no genetic sequencing was done to identify the relatedness of the RSV strains. This means we cannot be sure that all the subsequent infections within the household were directly related to the index case, suggesting that the secondary attack rate may be overestimated.

Basic reproduction number (R_0)

The basic reproduction number is "a measure of the number of infections produced, on average, by an infected individual in the early stages of an epidemic, when virtually all contacts are susceptible" (Porta, 2014). It is an epidemiologic metric used to describe the contagiousness or transmissibility of infectious agents in a population (Delamater et al., 2019). We found four studies which aimed to calculate the R_0 of RSV.

Study	Type	Period	Location	Mean R_0	95% CI
Duvvuri et al. (2015)	RSV-A ON-1	2011-2012	Ontario, Canada	1.03	1.007-1.07
Duvvuri et al. (2015)	RSV-A ON-1	2011-2012	Global	~1.01	1.011-1.032
Otomaru et al. (2019)	RSV-A	2014	Kawayan, Philippines	1.33	1.33-1.33
Otomaru et al. (2019)	RSV-A	2014	Caibiran, Philippines	0.92	0.92-1
Otomaru et al. (2019)	RSV-B	2014	Kawayan, Philippines	1.11	1.09-1.18
Otomaru et al. (2019)	RSV-B	2015	Kawayan, Philippines	1.04	0.90-1.25
Otomaru et al. (2019)	RSV-B	2015	Caibiran, Philippines	1.76	1.62-1.83
Reis and Shaman (2016)	RSV	2004-2014	USA	3.0	1.5-4
Reis and Shaman (2018)	RSV	2004-2014	USA	2.82 (peak)	not given

Table 3. Estimates of R_0 in all included studies

The included studies used different sources of data and varying methods in order to estimate R_0:

Study	Source of Data	Method of Calculation
Duvvuri et al. (2015)	**Ontario:** RSV A-positive specimens submitted to Public Health Ontario. **Global:** NCBI's GenBank Sequence Database	Used BEAST for genetic analysis of samples (G-gene sequences) from global dataset and from Ontario. Estimated R_0 based on exponential growth and logistic growth models.
Otomaru et al. (2019)	**Philippines:** Data collected through a community-based prospective cohort study. Note that swabs were only taken from symptomatic ARI cases,	Calculated R_0 using Wallinga-Teunis approach, based on data of daily new positive cases and date of onset of ARI. Derived serial interval (3.2 days,

	and that data was only collected on children <5 years old.	SD 0.35) from household analysis within the study.
Reis and Shaman (2016)	**USA:** Data from CDC, collected through the National Respiratory & Enteric Virus Surveillance System from 2004 onwards.	Used a susceptible-infectious-recovered (SIR) model, optimised using an ensemble adjustment Kalman filter (EAKF) together with ten years of US sample data.
(Reis & Shaman, 2018)	**USA:** Data from CDC, collected through the National Respiratory & Enteric Virus Surveillance System from 2004 onwards.	Used a susceptible-infectious-recovered (SIR) model, optimised using an ensemble adjustment Kalman filter (EAKF), and using US sample data to compare observed vs simulated outbreaks.

Table 4. Methods of calculating R_0 in all included studies

Quality and Generalisability of the Evidence

Only studies which used some real-world data in order to estimate R_0 were included in this review – pure modelling / simulation studies were excluded. Overall, the evidence base is fairly limited (a small number of studies, with limited geographical spread) and estimates of R_0 for RSV range from 0.92 (Otomaru et al., 2019) to 3.0 (Reis & Shaman, 2016). The quality of the included studies was generally moderate. Notably, in the data used by Otomaru et al. (2019), only symptomatic children were tested for RSV, meaning its results are likely to be significant under-estimates.

It is essential to interpret and apply R_0 values with a caveat. R_0 is multifactorial and is not a biological constant for a pathogen. It can have dissimilar values during different epidemics of the same virus (Froda & Leduc, 2014). It is affected by the environmental factors and behaviour of the infected population as well as pathogen characteristics. Otomaru et al. (2019) demonstrated the spatial and temporal variation in R_0 in their study by comparing R_0 estimates between two regions (Caibiran and Kawayan) for two years (2014 and 2015) in the under-5 population. It was concluded that the R_0 for RSV-B was high in Caibiran in 2015 and larger outbreaks were observed in 2015. Population demographics also contribute to the variability in R_0 values. Simple SIR or SIRS models are at risk of underestimating the R_0 values as it has been shown that models that account for age structure tend to produce higher estimates of R_0 (Pitzer et al., 2015; Weber et al., 2001; White et al., 2007)

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

In addition, R_0 applies to a population only when the entire population is susceptible to the disease – i.e. when no one is vaccinated or has had the disease before, or there is no means of controlling the disease spread. A combination of these conditions very rarely occurs in the case of RSV, as most children under five years are infected, and non-pharmaceutical interventions have been found to be effective in controlling the spread. The effective reproduction number, therefore, may be more relevant in the case of RSV as it measures the expected number of new infections caused by an infectious individual in a population where some individuals may no longer be susceptible to infection (Gostic et al., 2020).

Generation time

The **generation time**, or **serial interval**, is "the period of time between analogous phases of an infectious illness, in successive cases of a chain of infection, that is spread from person to person" (Porta, 2014). We found one study which calculated the serial interval of RSV.

Otomaru et al. (2019) conducted a prospective cohort study of children under 5 years old in the Philippines, from 2014 to 2016. Swabs were taken from children with symptomatic acute respiratory infection and tested for RSV. Otomaru et al. (2019) defined the serial interval as the duration between symptom onset of a primary case and symptom onset of a secondary case, and calculated this for 31 pairs of children within 29 households, finding an estimated serial interval of **3.2 days** (with 95% CI of 2.5-3.8 days using gamma distribution, 2.5-3.9 days using Weibull distribution, or 2.5-4.1 days using log-normal distribution).

Quality and Generalisability of the Evidence

Few conclusions can be drawn from a single study. This study did not test asymptomatic children, which is a relevant limitation in respect of some of its objectives (discussed in the context of R_0 above), but does not affect the calculation of the serial interval, as symptoms are central to the definition. However, the study did not investigate the genetic relatedness of the pairs which it considered to be index cases and secondary cases, and the overall sample size (31 pairs) is relatively small.

Viral shedding

We take **shedding** to mean the excretion of virus particles from the body via any bodily route. Shedding may be taken as a proxy for infectivity, for example when determining periods of isolation or quarantine; but this is not necessarily accurate, as studies have found that viral shedding can still be detected even when the virus that has been shed is no longer viable (Widders et al., 2020).

Duration of Shedding

We found 12 studies which looked at the duration of shedding:

Study	Type	Period	Setting	Sample	Location	Average duration of shedding	Range / prolonged shedding	How measured?
Agoti et al. (2019) *	RSV-B	Dec 2009 – Jun 2010	Community	130 infected participants (all ages)	Kilifi, Kenya	--	9 of 130 infected participants shed for more than 3 weeks	Positive sample obtained via multiplex real-time RT-PCR
Hall et al. (1979)	RSV	Jan-Mar 1977	Hospital (NICU)	23 infected neonates	New York, USA	9 days	Range: 3-22 days	Infants tested for RSV every 2-4 days using nasal washes & viral cultures
				18 infected staff	New York, USA	4 days	Range: 1-8 days	Samples taken & viral cultures done (fewer details provided)
P. K. Munywoki et al. (2015) *	RSV A and B	2009-2010 RSV season	Community	179 infected participants (all ages) with 205 infection episodes	Kilifi, Kenya	11.2 days (95% CI 10.1-12.3 days) *based on mid-point estimate*	24 participants shed RSV for 21 days or more *(41.7% of these were aged under 1 year)*	RSV infection confirmed by multiplex PCR on deep naso-pharyngeal swabs
Lehners et al. (2016)	RSV A and B		Hospital	64 infected immuno-	Heidelberg, Germany	--	16 px: 1-2 wks 10 px: 3-4 wks	Naso-pharnygeal

Study	Type	Period	Setting	Sample	Location	Average duration of shedding	Range / prolonged shedding	How measured?
		February 2013 onwards		compromised participants (adults)			8 px: 5-6 wks 2 px: 7-8 wks 6 px: ≥12 wks	samples tested with RT-PCR
				Subset of 16 ppts who shed for >30 days (adults)	Heidelberg, Germany	Median 80 days	35-334 days	
Geis et al. (2013)	RSV A and B	2011-2012	Hospital	57 hematology patients (adults)	Heidelberg, Germany	Median 24.5 days	1-168 days	Naso-pharnygeal samples tested with RT-PCR
Patrick K. Munywoki et al. (2015) *	RSV A and B	2009-2010 RSV season	Community	47 symptomatic index cases	Kilifi, Kenya	Mean 13.3 days (95% CI 10.67-15.89 days)	--	RSV infection confirmed by multiplex PCR on naso-pharyngeal swabs
				37 asymptomatic index cases	Kilifi, Kenya	Mean 6.8 days (95% CI 5.3-8.4 days)	--	
de Lima et al. (2014)	RSV	Aug 2011-Aug 2012	Hospital	3 transplant patients with confirmed RSV (adults)	Southern Brazil	13 days	3-23 days**	RSV infection confirmed by multiplex PCR on swabs from symptomatic patients
Wathuo et al. (2016) *	RSV	2009-2010 RSV season	Community	179 infected participants (all ages) with 208 infection episodes	Kilifi, Kenya	**Age <1 y** Median 15.5 days	IQR 9.5-24.5 days	RSV infection confirmed by multiplex PCR on naso-pharyngeal swabs
						1-<5 y Median 10.0 days	IQR 7.0-13.0 days	
						5-<15 y Median 7.0 days	IQR 4.0-10.5 days	
						15-<40 y Median 5.0 days	IQR 3.5-7.5 days	
						>= 40 y Median 14.0 days	IQR 3.5-14.3 days	
von Linstow et al. (2006)	RSV	Winter 2003-2004	Hospital	37 confirmed RSV positive children	Copen-hagen, Denmark	Median 11.5 days	IQR 6.5-18.5 days	Naso-pharyngeal, saliva, urine and faecal samples tested weekly by real-time RT-PCR
Silva et al. (2020)	RSV-A ON-1	May 2013	Hospital (NICU)	10 infected infants	Sao Paulo, Brazil	--	Longest shedding period: 29 days	Samples tested with RRT-PCR
	RSV-A NA-2	June 2013	Hospital (NICU)	14 infected infants	Sao Paulo, Brazil	--	Longest shedding period: 14 days	
Okiro et al. (2010)	RSV	Dec 2003-Jun 2004; Nov 2004-Mar 2005	Community	136 RSV-positive children with clinic records of # days with symptoms	Kilifi, Kenya	Mean duration 4.5 days (95% CI 4.0-5.3) Median duration 4 days	IQR 2-6 days Range 1-14 days	RSV confirmed by DFA tests of nasal washes. Day 0 of shedding taken as date of symptom onset (using clinic records); last day of

Study	Type	Period	Setting	Sample	Location	Average duration of shedding	Range / prolonged shedding	How measured?
								shedding = day of first -ve test
Hall et al. (1976)	RSV	Dec 1974-Mar 1975	Community	60 samples from 39 RSV-infected participants (all ages)	USA	Mean duration 3.4 – 7.4 days (3.9 days for under-16 and 1.6 days for over-16 year olds)	1 – 36 days	Viral cell culture of nose and throat cultures taken from participants every 3-4 days

Table 5. Duration of shedding in all included studies

**Studies worked with the same cohort of participants from Kilifi, Kenya*
***The study also refers to two patients with confirmed RSV who shed for 0 days (in addition to the three who shed for between 3 and 23 days); no further explanation is given.*

All ages

Five studies investigate the duration of RSV viral shedding among all age groups (Agoti et al., 2019; Hall et al., 1976; Patrick K. Munywoki et al., 2015; P. K. Munywoki et al., 2015; Wathuo et al., 2016) – with the exception of Hall et al. (1976), all of these worked with the same study cohort in Kilifi, Kenya. P. K. Munywoki et al. (2015) calculated an average shedding duration of **11.2 days**; finding, together with Agoti et al. (2019), that a small proportion of people shed for **more than three weeks**. Hall et al. (1976) estimated an average shedding duration between **3.4 – 7.4 days** (as samples were taken only every 3-4 days), with individual durations from 1 to 36 days.

Patrick K. Munywoki et al. (2015) analysed duration of shedding among **symptomatic and asymptomatic participants**, finding the mean duration of shedding to be 13.3 days among symptomatic cases (95% CI 10.67-15.89 days) and 6.8 days among asymptomatic cases (95% CI 5.3-8.4 days).

Children

Four studies (Hall et al., 1979; Okiro et al., 2010; Silva et al., 2020; von Linstow et al., 2006) looked at shedding duration among children only. Duration of shedding ranged from a **mean of 4.5 days** (Okiro et al., 2010) **to 11.5 days** (von Linstow et al., 2006), with shedding durations of up to 29 days recorded (Silva et al., 2020).

At face value, this is not so different from the findings for all ages (above). However, P. K. Munywoki et al. (2015) record that 41.7% of participants who shed for more than 21 days were infants under one year old. Similarly, based on an age-stratified analysis, Wathuo et al. (2016) found the longest durations of shedding among **infants under 1 year old (median 15.5, IQR 9.5-24.5 days),** as well as and adults over 40 years old (median 14.0, IQR 3.5-14.3 days). Hall et al. (1976) likewise found that children under 2 years old shed virus for significantly longer (mean **9 days**) than older participants.

This analysis, together with the finding in Okiro et al. (2010) that shedding ceases more rapidly among children who had previously been infected with RSV, suggests that **the very youngest children** (including those with their first RSV infection) contribute substantially to driving up the average duration of RSV shedding.

Immunocompromised adults

Three studies (de Lima et al., 2014; Geis et al., 2013; Lehners et al., 2016) examined shedding duration among immunocompromised transplant patients (all adults). Geis et al. (2013) found the median duration of shedding to be **24.5 days**; de Lima et al. (2014) found the average duration to be **13 days** (however, this was based on a sample of only three patients).

Although shedding durations range from as little as one day (Geis et al., 2013) or 1-2 weeks (Lehners et al., 2016), to as much as 334 days (Lehners et al., 2016), this group of people appears to include some very long-term viral shedders. For a subset of six patients who shed RSV for more than 30 days, Lehners et al. (2016) calculated their median duration of shedding to be **80 days**. They found that patients who had received a prior allogeneic transplant were more likely to shed for longer.

Volume of shedding

Two studies investigated the volume of RSV shed. Hall et al. (1979) measured the mean titre of RSV in the nasal washes taken from infants, and found that the amount of virus shed was correlated with **age at onset of infection,** and with the presence of **lower respiratory tract infection**.

Wathuo et al. (2016) plotted time concentration curves of different log-viral densities over the duration of an RSV episode. Their midpoint scenario assumed that shedding started halfway between the last previous negative sample and the first positive sample, and ended halfway between the final positive sample and the next negative one. The estimated median amount of RSV shed per episode was 41.7 $\log_{10}$ RNA copies (IQR 24.3-68.0).

As shown in Table 6 below, the volume of virus shed appears to be highest in **very young children (under 1 year old) and older adults (over 40 years old)** (p=0.001); among **symptomatic individuals** as compared to asymptomatic (p<0.001); and among people **coinfected with RSV-A and RSV-B** compared to people infected with a single strain (p=0.003). These reflect similar trends in the length of duration of shedding, discussed above.

Study	Setting	Sample	Sub-group	Amount shed	Units
Hall et al. (1979)	Hospital (NICU)	23 infected neonates	Aged under 3 weeks	2.0 (peak)	$\log_{10}$ $TCID_{50}$ per ml
			Aged over 3 weeks	3.8 (peak)	$\log_{10}$ $TCID_{50}$ per ml
Hall et al. (1979)	Hospital (NICU)	23 infected neonates	Lower respiratory tract infection	3.9	$\log_{10}$ $TCID_{50}$ per ml
			No lower respiratory tract infection	2.4	$\log_{10}$ $TCID_{50}$ per ml
Wathuo et al. (2016)	Community	179 infected participants (all ages) with 208 infection episodes	Age <1 year	71.0 (IQR 42.3, 96.7)	$\log_{10}$ RNA copies
			Age 1-<5 y	37.7 (IQR 24.6, 54.4)	$\log_{10}$ RNA copies
			Age 5-<15 y	25.0 (IQR 14.1, 36.7)	$\log_{10}$ RNA copies
			Age 15-<40 y	14.6 (IQR 9.4, 32.4)	$\log_{10}$ RNA copies
			Age >= 40 y	56.3 (IQR 5.7, 65.3)8	$\log_{10}$ RNA copies
Wathuo et al. (2016)	Community	179 infected participants	Symptomatic cases	42.5 (IQR 25.1, 66.0)	$\log_{10}$ RNA copies

		(all ages) with 208 infection episodes	Asymptomatic cases	19.0 (IQR 9.8, 29.0)	log_{10} RNA copies
Wathuo et al. (2016)	Community	179 infected participants (all ages) with 208 infection episodes	RSV-A only	26.4 (IQR 15.1, 52.4)	log_{10} RNA copies
			RSV-B only	28.8 (IQR 13.2, 48.9)	log_{10} RNA copies
			RSV-A/B coinfection	66.1 (IQR 42.1, 75.5)	log_{10} RNA copies

Table 6. Volume of shedding in all included studies

Quality and Generalisability of the Evidence

The studies cover a range of different locations (Brazil, Denmark, Germany, Kenya and the USA) and diverse groups of participants. Four papers draw on data from the same cohort study in Kilifi, Kenya; so care should be taken not to overstate the breadth of the evidence base. With one exception, studies have taken place within the last twenty years, with up-to-date techniques for sampling and detecting RSV. On the whole, although a number of studies distinguish between RSV-A and RSV-B infections in their description of the study sample, most do not distinguish between RSV strains in their analysis of shedding duration. The overall quality of the studies is moderate to high, although three studies (Hall et al., 1979; Silva et al., 2020; von Linstow et al., 2006) had more significant limitations due either to transparency or consistency of methods.

Mode of transmission

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

We found 13 studies exploring the mode of transmission of RSV. Eight looked at transmission by direct or indirect contact (Agoti et al., 2017; Hall et al., 1981; Hall & Douglas, 1981; Heikkinen et al., 2015; Meissner et al., 1984; Pappas et al., 2010; van de Pol et al., 2010; Zhu et al., 2017) and seven at transmission by airborne routes (Chamseddine et al., 2021; Grayson et al., 2017; Hall & Douglas, 1981; Kulkarni et al., 2016; Kutter et al., 2021; Thorburn et al., 2004; van de Pol et al., 2010).

Direct or indirect contact

There is very limited direct evidence or measurement of transmission via direct contact or fomite. Five studies used various methods to examine patterns of transmission within households (Agoti et al., 2017; Heikkinen et al., 2015) or hospital settings (Hall & Douglas, 1981; Meissner et al., 1984; Zhu et al., 2017), and inferred that person-to-person transmission is likely.

One further study (van de Pol et al., 2010) found an absence of RSV transmission in the presence of standard infection control measures designed to prevent contact, fomite or droplet-based transmission; suggesting that these are therefore the most likely modes of transmission for RSV. However, these studies do not confirm direct or fomite transmission of RSV, and do not rule out airborne transmission.

Two studies attempted to measure RSV transmission more directly. In an experimental study in which volunteers were administered RSV inoculum by one of three routes (nose, eyes or mouth), Hall et al. (1981) found that participants who received RSV by their nose or eyes were much more likely to be infected than participants who received it by mouth. Pappas et al. (2010) took swabs

from used and new toys in GP waiting rooms during the peak of RSV season, and did not find any evidence of RSV RNA – providing no evidence for transmission by the fomite route.

Study	Dates	Location	Population	How was transmission measured?	Findings
Agoti et al. (2017)	Dec 2009-Jun 2010	Kilifi, Kenya	13 households	Genomic analysis and continuous testing used to track possible chains of infection within households	7/9 households where sequencing was sufficient showed household-specific genomic variation indicating that direct transmission between household members was likely.
Hall et al. (1981)	(not given)	New York, USA	32 adult volunteers	RSV inoculum administered via three routes: nose, eyes and mouth	Authors interpret that nose and eyes are equally sensitive to infection by RSV, but mouth is relatively insensitive.
Hall and Douglas (1981)	(not given)	New York, USA	31 young adult volunteers	3 groups: 7 "cuddlers" provided direct care to an infected infant for 2-4 hours (without gloves or mask); 10 "touchers" touched contaminated surfaces and then their own faces; 14 sitters sat >6 feet from the bed of an infected infant for three hours.	5/7 "cuddlers" and 4/10 "touchers" were infected. Authors interpret that transmission by direct contact or by touching contaminated surfaces is possible, but found no evidence of airborne transmission (no "sitters" infected).
Heikkinen et al. (2015)	2005-06 RSV season	Turku, Finland	52 families of hospitalised children	Families of RSV-infected children were tested for infection; questionnaires used to establish when symptoms started	In 30 families (58%) a parent or sibling was found to be the probable primary case of RSV.
Meissner et al. (1984)	Winter 1981-82	Boston, Massachu-setts	9 infants in a newborn nursery	A map of the ward layout and the locations of infected infants was drawn to identify possible clusters of infection	Infants with the same infection tended to be in adjacent beds, suggesting person-to-person transmission.
Pappas et al. (2010)	(not given)	Virginia, USA	Toys (hard surfaces)	Swabs were taken from toys in children's waiting rooms in a GP practice during January (peak RSV season)	No RSV RNA was found on any of the sampled toys.
van de Pol et al. (2010)	2005-06 RSV season	Utrecht, Netherlands	Children in PICU ward	Whenever an RSV-infected child was admitted, other children were tested on admission and every 5 days for infection. Standard infection control procedures were in place.	No new cases of RSV were detected during any of the sampling periods; implies effectiveness of infection control measures designed to prevent contact, fomite and droplet transmission.
Zhu et al. (2017)	2015	Illinois, USA	11 hospital patients and 5 staff (adults)	Phylogenetic analysis of samples taken from infected patients to examine genetic relatedness of their RSV-B infections.	11 of 19 samples were identified as being genetically related. Healthcare workers found likely to be important in transmission of RSV between patients.

Table 7. Studies of contact- and fomite-based transmission of RSV

We also note the findings of von Linstow et al. (2006), discussed in the section on viral shedding above. This study did not directly examine transmission of RSV, but collected samples of various bodily fluids from children infected with RSV. They detected RSV in 68% (n=26) saliva samples; in stool samples from 5 children (13.9%); and in sweat samples from 3 children (8.8%). No RSV was detected in urine or blood samples.

Airborne transmission (droplet and aerosol)

Two studies (Thorburn et al., 2004; van de Pol et al., 2010) inferred the likelihood of droplet-based transmission because nosocomial infections of RSV reduced following reinforcement of hospital infection control measures designed to prevent droplet-based transmission.

Four studies tried to measure airborne transmission by sampling the air from healthcare settings with RSV-infected patients. Of these, three studies (Chamseddine et al., 2021; Grayson et al., 2017; Kutter et al., 2021) found that **airborne transmission was likely to be an inefficient route of transmission** for RSV; and detected RSV only in larger droplet particles, rather than smaller aerosol particles. By contrast, Kulkarni et al. (2016) found high quantities of viable RSV in small particles at

1m from infected patients' heads, providing some evidence for airborne transmission of RSV. One study (Hall & Douglas, 1981), discussed in the section above, tested for the possibility of airborne transmission by sitting volunteers >6 feet from the bed of infected infants, with no direct contact with the infant or contaminated surfaces, and found no evidence of transmission occurring.

Study	Dates	Location	Population	How was transmission measured?	Findings
Chamseddine et al. (2021)	Jan-Mar 2018	Beirut, Lebanon	3 hospital in-patients with RSV	Air samples were collected from the rooms of infected patients, at 0.30m and 2.20m from their heads. Samples were collected using the Coriolis µ Biological Air Sampler and tested using RT-PCR.	RSV was not detected in the air samples from the rooms of any of the RSV+ patients.
Grayson et al. (2017)	(not given)	West Virginia, USA	554 air samples from paediatric clinic	554 air samples were taken over 48 days from two paediatric examination rooms. Samplers were set at 102cm and 152cm above floor level. 2-stage bioaerosol cyclone samplers were used, and RSV was tested for using real-time PCR.	13/554 samples (2.3%) were positive for RSV. Over 90% were above 4.1µm in size (droplets); only one sample (8%) was in the 1-4.1µm size range. Authors conclude that airborne transmission is likely to be highly inefficient for RSV.
Kulkarni et al. (2016)	(not given)	Leicester, England	24 infants (on ward) + 10 infants (in CICU)	Air samples were taken at 1m, 5m and 10m from the heads of infected infants, using the Westech 6-stage Microbial Sampler. RSV was confirmed using PCR. Viable RSV was tested for using viral cell cultures and immunofluorescent staining.	A mean number of plaque-forming units of 315,189 (±313,714 SD) was found in particles at 1m from infected infants in the ward; 220,011 (±190,075 SD) in particles <4.7µm – a size likely to be inhaled into the lower respiratory tract. There was a significant reduction 5m away from index cases, and no RSV was detected at 10m away.
Kutter et al. (2021)	Nov 2017-Apr 2020	Delft, Netherlands	6 infants	Air in single-patient rooms sampled daily for 30 minutes. Samples collected by 6-stage Andersen impactor; tested for RSV using qRT-PCR. Viral cell cultures and immunofluorescence assays used to test for infectiousness of RSV.	Low amounts of RSV were detected in the air around 3 (of 6) RSV patients. RSV was only detected in large (>7µm) droplets. Infectious virus was not detected.
Thorburn et al. (2004)	Oct-Mar 2002	Liverpool, England	54 RSV+ children on PICU ward	Nosocomial infections of RSV were monitored throughout the season using ELISA membrane tests.	Nosocomial transmissions reduced following reinforcement of droplet infection control measures, suggesting that droplet transmission is a likely route of hospital-based infection.
van de Pol et al. (2010)	2005-06 RSV season	Utrecht, Netherlands	Children in PICU ward	Whenever an RSV-infected child was admitted, other children were tested on admission and every 5 days for infection. Standard infection control procedures were in place.	No new cases of RSV were detected during any of the sampling periods; implies effectiveness of infection control measures designed to prevent contact, fomite and droplet transmission.

Table 8. Studies of airborne transmission of RSV

Study Quality and Risk of Bias

Study quality was variable, although studies designed to test airborne transmission of RSV were generally of higher quality than those relating to other routes of transmission. The great majority of studies took place in high-income countries, in various healthcare settings. This limits generalisability to community settings and lower-income contexts. While Agoti et al. (2017) is an important exception, taking place in a community setting in rural Kenya, this study demonstrates that within-household transmission is likely, but does not identify the method by which such transmission may take place.

It is important to note that Kulkarni et al. (2016) found a high likelihood of airborne transmission of RSV, in contrast to all the other included studies of airborne transmission. We did not find any

obvious flaws in the methodology of any of these studies which would explain the differences between them; nor are the authors of a more recent study able to explain the difference (Kutter et al., 2021). This suggests that this potential transmission mechanism would benefit from further study.

DISCUSSION

The aim of this rapid review was to synthesise evidence on ten different epidemiological parameters in respect of RSV, in order to inform planning for future outbreaks of the disease. In practice, the information we found about these parameters was limited and of variable quality. Study findings were heterogeneous, with respect to participant characteristics (especially age and comorbidities) and methods of calculation of the parameter of interest, and do not lend themselves to meta-analysis.

Detection versus Infection

A small number of studies of airborne transmission of RSV (Kulkarni et al., 2016; Kutter et al., 2021) tested samples for the presence of RSV using RT-PCR, and followed this up by testing for infectiousness using viral cell cultures. The majority of other studies tested for RSV using PCR testing only, and did not distinguish between the presence of RSV and its infectiousness. This may be particularly relevant in respect of the mode of transmission and the duration and volume of viral shedding: without knowing whether the virus that is shed or transmitted is still infective, current estimates of these parameters may overstate the risk.

Gaps in the Evidence Base

We found no studies at all in respect of four parameters of interest (incubation period, latency period, duration of infectiousness, and doubling time). However, we would draw attention to a systematic review by Lessler et al. (2009) which estimates the **incubation period** of RSV, together with other respiratory viruses. We were unable to access the three original studies from 1961 and 1966 which informed their estimate. The information given within the systematic review indicates some important limitations to those studies, particularly with respect to sample size and study conduct: with 7 observations from infants and young children in total, across two studies, and 17 from one study with young adults alternately described as “volunteers” or “inmates”. Nevertheless, Lessler et al. (2009) obtained a pooled estimate of the mean incubation period of RSV as **4.4 days** (95% CI 3.9-4.9 days).

For the parameters we were able to include, we found that the overall evidence base was generally quite limited (only one study provided an estimate of the serial interval or of the secondary attack rate). The majority of studies focused on infants and young children, or on immunocompromised adults (specifically transplant recipients); and most studies took place in hospital or other healthcare settings. Several papers draw on the same study in Kilifi, Kenya; which provides valuable information about RSV transmission in a rural, low-income, community setting, by contrast to most of the other studies included. However, as most of our knowledge about transmission in low-income, community settings comes from that one study, care should be taken not to overstate it.

The quality of studies related to contact- and fomite-based transmission of RSV was notably poor, with a number of studies simply deducing the mode of transmission from the effectiveness or otherwise of infection control provisions. Studies of airborne transmission were generally more sophisticated, with some important unresolved disagreements between studies about the likelihood

of transmission via this route. Further, well-conducted studies of the different modes of transmission of RSV would be valuable.

Strengths and Limitations of the Review

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

Although no time cut-off was applied to our searches, it is possible that older studies related to RSV may have been missed due to more limited online availability or incomplete archiving. A more extensive systematic review, incorporating a wider range of databases and snowballing from included studies, might identify more of these older, seminal pieces of research.

However, this approach enabled us to conduct a thorough review within a short timeframe, in order to provide a summary of the best-available evidence, which may be used to inform the assumptions underpinning future planning for the management of RSV outbreaks. To the best of our knowledge, no other rapid or systematic reviews have been published on this topic so far.

Implications for Research, Policy and Practice

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

It has also identified that the current evidence base is significantly limited. More good-quality studies are needed to inform our understanding of all the key parameters of interest; particularly studies in lower-income countries, in non-healthcare settings, and among all age groups. Robust, high quality studies of modes of transmission in nosocomial settings are also needed, to inform effective risk management.

CONCLUSIONS

There is limited overall evidence on key epidemiological parameters of RSV. We have synthesised evidence on the attack rate, secondary attack rate, R0, serial interval, duration and volume of shedding, and modes of transmission of RSV, and have reported on previous work to estimate the incubation period; all of which may usefully inform planning assumptions for the future management of RSV outbreaks. We found no evidence in respect of the latency period, duration of infectiousness, or doubling time. Overall study quality was variable, with a small number of well-conducted studies contributing significantly to our understanding of this area; and substantial further high-quality research would be beneficial, across all parameters of interest.

APPENDICES

Appendix 1: Review Protocol

1. Review title

What are the parameters (attack rates, generation intervals, latent period, incubation period, duration of infectiousness, reproduction number) and modes of transmission of RSV [respiratory syncytial virus]?

2. Search strategy

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

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to April 19, 2022>

1	exp Disease Transmission, Infectious/
2	transmission.fx.
3	infections/ or exp cross infection/
4	(transmi* or serial interval or reproducti* number or reproducti* ratio).ti,ab.
5	1 or 2 or 3 or 4
6	Respiratory Syncytial Virus Infections/
7	respiratory syncytial viruses/ or respiratory syncytial virus, human/
8	(respiratory syncytial virus* or rsv).ti,ab.
9	bronchiolitis/ or bronchiolitis, viral/
10	bronchiolit*.ti,ab.
11	6 or 7 or 8 or 9 or 10
12	5 and 11

Prior systematic reviews will be scrutinised for relevant included studies.

3. Selection Criteria

	Include	**Exclude**
Population	Any (human)	Animal studies
Exposure	RSV (lab-confirmed)	ILI or SARI Bronchiolitis [in the absence of lab-confirmed RSV] Any other virus / condition
Comparator	N/A	N/A
Outcome	• **Attack rate(s)** • **Generation interval(s)** • **Latent period & incubation period** • **Duration of infectiousness** • **Reproduction number** • **Doubling time / growth rate** • **Mode(s) of transmission**	Symptomatology Risk factors for transmission % symptomatic Zoonotic transmission

Study types	Observational epidemiological studies RCTs and quasi-experimental studies	Case series & case reports Animal studies In-vitro studies Modelling studies Papers with no data (commentaries, etc)
Language	English	Languages other than English
Setting	Any	None
Geographical location	Any	None
Timeframe	Any	None

4. Screening

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

5. Data Extraction

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

- Title
- Author(s)
- Study type
- Year published
- Dates of study
- Country
- Setting
- Study population size
- Relevant covariates e.g.
    - Age
    - Gender
    - Race or ethnicity
    - Underlying conditions
    - Occupation
    - Socioeconomic status
    - Any coinfections
    - Vaccination status (RSV)
- Exposure(s)
    - RSV subtype (A/B)
    - RSV strain
- Diagnostic test(s) used
- Outcome [with confidence intervals]:
    - Attack rate(s)
    - Generation interval(s)
    - Latent period
    - Incubation period
    - Duration of infectiousness
    - Reproduction number

    - Mode(s) of transmission
- Study conclusions
- Study limitations

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

6. Quality Assessment

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

7. Strategy for data synthesis

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

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

8. Subgroup analysis

If possible, we will analyse our findings separately for:

- RSV A and RSV B
- Pre- and post- November 2019 (before vs during the COVID-19 pandemic)
- Different age groups
- Settings (community / hospital)

Appendix 2: Search Strategy

Embase (Ovid) <1980 to 2022 Week 17>
Date of search: 5 May 2022
Results total: 1716

1	exp disease transmission/	223283
2	(transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab.	660729
3	1 or 2	766615
4	respiratory syncytial virus infection/	6627
5	human respiratory syncytial virus/ or human respiratory syncytial virus a/	6758
6	(respiratory syncytial virus* or respiratory syncitial virus* or rsv).ti,ab.	24223
7	exp bronchiolitis/	24094
8	bronchiolit*.ti,ab.	18086
9	4 or 5 or 6 or 7 or 8	49611
10	3 and 9	1716

Global Health (Ovid) <1973 to 2022 Week 17>
Date of search: 5 May 2022
Results total: 574

1	exp disease transmission/	163020
2	(transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab.	186343
3	1 or 2	283401
4	human respiratory syncytial virus/	6479
5	(respiratory syncytial virus* or respiratory syncitial virus* or rsv).ti,ab.	8142
6	bronchiolitis/	1914
7	bronchiolit*.ti,ab.	2755
8	4 or 5 or 6 or 7	10015
9	3 and 8	574

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to May 04, 2022>
Date of search: 5 May 2022
Results total: 1001

1	exp Disease Transmission, Infectious/	78381
2	transmission.fx.	160296
3	(transmi* or serial interval or reproducti* number or reproducti* ratio or R0).ti,ab.	586573
4	1 or 2 or 3	696326
5	Respiratory Syncytial Virus Infections/	8058
6	respiratory syncytial viruses/ or respiratory syncytial virus, human/	9519
7	(respiratory syncytial virus* or respiratory syncitial virus* or rsv).ti,ab.	19358
8	bronchiolitis/ or bronchiolitis, viral/	5402
9	bronchiolit*.ti,ab.	11862
10	5 or 6 or 7 or 8 or 9	31335
11	4 and 10	1001

Appendix 3: Non-JBI Quality Appraisal Checklists

UNCOVER Checklist for Experimental Studies

Appraisal Question	Yes / No / Unclear / NA
Was the study performed in line with the stated methodology/protocol?	
Is there a hypothesis/ aim stated?	
Are the statistical tests appropriate for level of data and hypothesis being tested?	
Were the statistical analyses performed correctly?	
Was all data presented with no missing data?	
Does the data justify the conclusion/ outcomes?	
Are the results from this study generalisable and applicable to non-experimental settings?	
What were the study's methodological limitations?	
Did the authors make any suggestions for future research?	

Adapted CHARMS Checklist

The CHARMS checklist is designed for quality appraisal of clinical prediction models for inclusion in systematic reviews (Moons et al., 2014). We adapted it in order to use it for quality appraisal of studies which develop statistical models using real-world data in order to predict R0. Where we have adapted or removed questions, this is shown in square brackets in the table below.

Appraisal Question		**Response**	
Domain	**Key Item**	**How did the study address this?**	**Does this raise any concerns? (Y,N,N/A)**
Source of Data	Source of data (e.g. observational study, RCT ppts, registry data)		
Participants	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)		
	Participant description		
	Details of treatments received, if relevant		
	Study dates		
Outcome(s) to be Predicted	Definition and method for measurement of [R0]		
	[other items not used]		
Candidate Predictor(s)	[items not used]		
Sample Size	Number of participants		
	[item not used]		
Missing Data	Number of participants with any missing data		

	Handling of missing data (e.g. complete-case analysis, imputation, etc)		
	[other items not used]		
Model Development	Modelling method		
	Modelling assumptions satisfied		
	[other items not used]		
Model performance	[new] How does the model perform?		
	[items not used]		
Model evaluation	Method used to test performance (e.g. development dataset or external validation)		
	In case of poor validation, whether model was adjusted or updated		
Results	Final and other models presented		
	[other items not used]		
Interpretation / Discussion	Interpretation of presented model/s		
	Comparison with other studies, discussion of generalisability, strengths & limitations		

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