



## **SCIENTIFIC** ADVICE

# Systematic review on the incubation and infectiousness/ shedding period of communicable diseases in children

**ECDC** SCIENTIFIC ADVICE

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Ida Czumbel with significant input from Pierluigi Lopalco, and produced by Pallas Health Research and Consultancy, Rotterdam.

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# Abbreviations

CDC	US Centers for Disease Control and Prevention
CoCanCPG	Coordination of Cancer Clinical Practice Guidelines
EU/EEA	European Union/European Economic Area
<i>E Coli</i>	<i>Escherichia coli</i>
EIEC	Enteroinvasive <i>Escherichia coli</i>
EHEC	Enterohemorrhagic <i>Escherichia coli</i>
EPEC	Enteropathogenic <i>Escherichia coli</i>
ETEC	Enterotoxigenic <i>Escherichia coli</i>
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
STEC/VTEC	Shiga-toxin/verocytotoxin producing <i>E. coli</i>
WHO	World Health Organization

# Glossary

Definition of infection-related key variables as provided by ECDC	
Incubation period (or latent period)	The time interval between invasion by an infectious agent and appearance of the first signs or symptoms of the disease in question. Includes specification of the relevant sign or symptom because some diseases have several symptoms with different timing, which would result in a different definition of incubation period.
Serial interval	The period of time between analogous phases of an infectious illness in successive cases of a chain of infection that is spread person to person.
Period of infectiousness (or period of communicability)	The time interval during which an infectious agent may be transferred directly or indirectly from an infected person to another person.
Duration of shedding	Period during which a patient excretes the organism (time from the onset of clinical disease).
Exclusion period	Minimum recommended period for which patients should be excluded from school or other childcare setting.
Study design definitions	
Randomised controlled trial (RCT)	An experimental study in which participants (or clusters) are randomly allocated to receive either intervention or control
Non-randomised controlled trial	An experimental study in which participants are allocated to receive either intervention or control (or comparison intervention) but the allocation is not randomised
Cohort study	An observational study in which a group of people is observed over time in order to see who develops the outcome of interest
Surveillance study	The study of all aspects of occurrence and spread of a disease that are pertinent to effective control, by means of ongoing systematic collection, analysis, interpretation, and dissemination of health data
Case-control study	A comparative observational study in which the investigator selects people who have an outcome of interest (for example, developed a disease) and others who do not have it (controls), and then collects data to determine previous exposure to possible causes.
Cross-sectional study	An observational study in which the source population is examined to see what proportion has the outcome of interest, or has been exposed to a risk factor of interest, or both, at a fixed time point.
Case series	A collection of patients with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, or diagnostic procedure.
Outbreak investigation (may be special form of case series)	Outbreak: The occurrence of more cases than expected in a particular population, in a specific geographical area and in a specified period of time. Outbreak investigation: any study of an outbreak.
Case report	Detailed description of a single patient or clinical case.
Attack rate	The cumulative incidence of infection in a group observed over the period during an epidemic. It can be determined empirically by identifying clinical cases and/or by means of seroepidemiology. Because its time dimension is uncertain or arbitrarily decided, it should not be described as a rate.

# Executive summary

## Objectives

Currently, there is no common European Union (EU) approach to the control of communicable diseases in schools or other childcare settings, e.g. by exclusion policies. To support the development of such an approach based on the best available relevant scientific information, a systematic literature review was performed of three key parameters: 1. incubation period; 2. period of infectiousness and/or the duration of shedding; and 3. exclusion period for 30 of the most common childhood infections or those of particular concern.

## Methods

We performed a search in PubMed and Embase (May–June 2015) using strings for:

- the selected infections
- children aged 1 month to 18 years
- incubation period
- period of infectiousness or shedding
- setting-specific exclusion period
- studies investigating humans.

No language, time, geographical or study design restrictions were applied. The resulting references were first screened for relevance by title and abstract using predefined in- and exclusion criteria. Those selected were further screened in full text for eligibility. In addition, full text articles were screened for relevant references (i.e., hand search) and these were also screened in full text for eligibility. From the selected references, the outcomes of interest and relevant study characteristics were extracted and presented, subdivided in five disease groups:

- vaccine preventable diseases (measles; meningococcal disease; mumps; pertussis; rubella; varicella);
- food and waterborne diseases (enterovirus infections; viral gastroenteritis by adenovirus, astrovirus, noro-/calici-/sapovirus, rotavirus; hepatitis A; campylobacteriosis; *Escherichia coli* infections; *Salmonella* infections (non-typhoid, typhoid, paratyphoid); shigellosis; giardiasis);
- airborne diseases (influenza; infectious mononucleosis; respiratory syncytial virus infections; streptococcal infections (scarlet fever, streptococcal pharyngitis, impetigo);
- other transmissible diseases of interest in pediatrics (roseola infantum, erythema infectiosum, staphylococcal impetigo, hospital colonization by resistant pathogens and MRSA infections).

Study specific basic quality issues were noted. Besides the information from scientific journal articles, we also searched websites of key institutions and relevant handbooks for the key parameters.

## Results

The search identified 12 617 references. Of those, 748 were selected for full text screening. In addition, 226 articles resulting from hand search were selected for full text screening. In total, 974 articles were selected for full text screening of which 171 were not retrieved and 691 were excluded with reason, such as ineligible outcomes, ineligible age and lack of stratified data. A total of 112 articles with relevant information were included in the review. Nineteen studies were included for vaccine-preventable diseases, of which most were for measles and none for meningococcal disease. For food- and waterborne diseases, 71 studies were included (most for noro/calicivirus and none for paratyphoid fever). For airborne diseases, 18 studies were included (most for Respiratory syncytial virus (RSV), none for streptococcal impetigo). For other transmissible diseases of interest in pediatrics, two studies were identified for roseola infantum, but none for erythema infectiosum or staphylococcal impetigo. No studies were identified for hospital colonisation by resistant pathogens or MRSA infections.

Furthermore, the results showed a remarkable diversity in study characteristics such as population age, symptomatology, treatment, vaccination, diagnostic tools, viral load, study design and reporting of key definitions.

Settings varied and included schools, daycare centres, households, institutions and hospitals. Study designs included outbreak investigations, laboratory-based case series, prospective surveillance studies and clinical trials. In addition, information was reported from two websites (Centers for Disease Control and Prevention, World Health Organization), two handbooks (the 'Red Book' and 'Managing disease in childcare and schools: a quick reference guide', both published by the American Academy of Pediatrics) and a publication from 2001 on the same topic by Richardson et al., 2001 [115].

Vaccine-preventable diseases were the most complete group in terms of the study parameters. Incubation period was available for each of the searched diseases. Period of infectiousness was missing, but even for these diseases, period of shedding was reported.

The incubation period was generally reported in terms of enteral diseases, however viral infections were more documented than bacterial infections in terms of study parameters. Regarding period of infectiousness and shedding, the parameters were generally reported with the exception of hepatitis A.

The searched parameters for airborne diseases were less often reported, however similarly to other disease groups, period of shedding was the most reported parameter (seasonal influenza, RSV and mononucleosis).

The parasitic infections (*Giardia*) and diseases listed under other diseases common among children were poorly documented.

## Conclusions

This project explores a little investigated public health issue of considerable importance. The study determined the incubation period, shedding, and infectiousness for the predefined disease categories. These findings have implications for the temporary school exclusion of children with an infectious disease. They provide evidence essential for public health action, such as the minimum period required for a school leave, and provide the evidence base for a guidance on the exclusion-making process. Although there were certain limitations to our study, the findings are nevertheless important and could serve as a good basis for the development of an evidence-based document on minimum school leave for an infectious disease in unjustifiable absences, and other strategies to control the spread of infectious diseases in childcare settings in Europe.

The conclusions of this study can be further strengthened by applying stringent methodological standards such as experimental study designs to test the public health benefits of school exclusion in relation to incubation period, period of infectiousness and shedding. Insights from such studies can be incorporated into an updated guidance document in the future.

# 1. Background

## 1.1 Introduction

Infectious diseases are caused by pathogenic microorganisms such as bacteria, viruses and parasites. Some infectious diseases are communicable from one person to another, for example by droplets, air suspensions, faeces, urine or skin-contact. Illnesses caused by infectious diseases are common in children in school or other childcare settings. Limiting the spread of disease in these settings is desirable.

Currently, there is no common EU approach with regard to the control of communicable diseases in school or other childcare settings and the reliability of the existing information is uncertain. A public health guidance aiming to control childhood infections, e.g. by exclusion policies, would allow for a better understanding of these infections in practice and enable the design of more effective public health interventions. The optimal control of communicable diseases requires information on incubation period and period of infectiousness of communicable diseases, as well as the effectiveness of control measures (e.g. of the period a child is excluded from the setting). Evidence from scientific literature can be used to develop a structured and evidence-based European guidance on the control of the most frequent communicable diseases in infants and teenagers that account for the majority of disease outbreaks and absenteeism in school or other childcare settings. Literature research can also identify the strengths and weaknesses of our knowledge in epidemiology of infectious diseases, highlighting areas for which the required information is missing and further research is required and eventually more resource investment is needed.

This report presents the combined results of a basic systematic literature search performed in August 2014 and an extended search performed in May/June 2015.

## 1.2 Scope and objectives

The purpose of this assignment is to collect, review and appraise, in a transparent and systematic way, using generally accepted evidence-based principles, the best available evidence and scientific knowledge on:

- incubation period (objective 1)
- period of infectiousness and/or the duration of shedding (the latter to be used to estimate the period of infectiousness when direct information is missing) (objective 2)
- exclusion period, when available (objective 3) of predefined infectious diseases which include the most common transmittable childhood infections or those of particular concern.

Its results are meant to provide ECDC with evidence for defining the minimum exclusion periods from schools or other childcare settings for the period of communicability of an infectious disease. This document could be used by countries in the European Union and the European Economic Area (EU/EEA), to help limit the spread of infectious diseases.

## 1.3 Outline of this report

In Chapter 2, the systematic review process is described. Results of the review process are described in Chapter 3. Results from the peer-reviewed literature and other data sources are described in Chapter 5 and 6, respectively. Discussion points are raised in Chapter 7. Conclusions are provided in Chapter 8. In the appendices we present the diseases and their categorisation, the PICO questions<sup>1</sup>, the search strategy, the checklist for quality appraisal, the exclusion list, the list of references that were not retrieved and the extraction tables.

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<sup>1</sup> Questions that include four parts, referred to as PICO that identify the patient problem or population (P), intervention (I), comparison (C) and outcome(s) (O).



## 2. Review methods

Pallas Health Research and Consultancy, performed a systematic literature review to identify the best available evidence and scientific knowledge on incubation period, period of infectiousness or shedding, and exclusion period of predefined infectious diseases.

A systematic review is an overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardised methods to identify and critically appraise relevant research, and to collect, report, and analyse data from the studies that are included in the review.

First, a basic systematic literature search was performed in August 2014. Because of significant gaps in evidence based on this search, an extended search was performed in May/June 2015 (including additional search terms for objective 2 and a second literature database). Below, the methods are described for the combination of both systematic reviews (basic and extended).

### 2.1 Research questions

The PICO method was used to specify the following research questions:

- Objective 1: What is the **incubation period** of specified transmittable infection diseases in children and teenagers?
- Objective 2: a) What is the **period of infectiousness** (or communicability) of specified transmittable diseases in children and teenagers? Or, if not available,  
b) What is the **duration of shedding** of specified transmittable diseases in children and teenagers?
- Objective 3: What is an appropriate or effective **exclusion period** for children and teenagers attending a school or other childcare setting infected with specific transmittable diseases?

The review focuses on the most common transmittable childhood infections or those with a particular concern.

The key variables from the three objectives are defined in the glossary.

### 2.2 Literature search strategy

#### Data sources

##### *Data sources for peer-reviewed literature*

For this literature review, two databases were searched:

- PubMed, the largest and most accessible database (<http://www.ncbi.nlm.nih.gov/pubmed/>).
- Embase, the well-known biomedical database containing more European journals (<http://www.embase.com>).

##### *Other data sources*

Other data sources included grey literature and any other source that may yield relevant information. Grey literature is defined here as: Information produced on all levels of government, academia, business and industry in electronic and print formats not controlled by commercial publishing i.e. 'where publishing is not the primary activity of the producing body'. The main other data sources of interest to ECDC were the websites of the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). In addition, hand search and google were used to identify (evidence-based) guidelines and recommendations for underlying references or relevant recommendations that were not identified in the peer-reviewed search.

#### PubMed search strings

The following preliminary search strings were composed and combined to yield the relevant references for further screening:

- terms for infectious disease
- terms for population: children and teenagers 1 month–18 years old
- terms for incubation period
- terms for period of infectiousness and shedding
- terms for setting-specific exclusion period

For each objective a search was performed, combining all diseases. Details on the search strings and the search strategy can be provided upon request.

Due to expected overlap between the three objectives, all references were combined for the first screening phase and the relevant full text publications were subdivided into separate diseases in the second screening phase.

### Limits

The use of limits increases the specificity of the search and decreases the number of hits.

Ready-made database limits for human studies were not used as previous experiences have indicated that these limits may rule out relevant articles. To limit the results to human studies (but including the studies presenting both human and animal data) the following search string were added, using NOT:

- Animals NOT (humans AND animals)

No time, language, geographical or study design limits were applied for this review, in order not to miss any relevant articles. The Embase search was focused on original research papers (i.e., publication type restricted to 'article' and 'article in press') to improve the efficiency of screening.

### Running the literature search

The final searches in PubMed and Embase were run on 26 May 2015 and 1 June 2015, respectively.

The searches were saved into a PubMed NCBI account and Embase account, respectively. Output, including all indexed fields per hit (e.g. title, authors, abstract), was exported to Endnote version X7.3. The source of the database (PubMed or Embase) was marked in Endnote.

### Hand search

Reference lists of relevant (narrative or systematic) review articles, key reports and included studies were searched for further potentially relevant articles or other relevant literature sources.

### Search in other data sources

The PubMed and Embase references screened for publications were not peer-reviewed research articles. In addition, the following searches were performed:

- A search for evidence-based guidelines on the websites of CDC (<http://www.cdc.gov/>) and WHO (<http://www.who.int/en/>), throughout the month of October 2014. This did not yield actual guidelines with sourced incubation periods and/or periods of infectiousness for the infectious diseases in this review.

Therefore, from the CDC-website we searched

- the Pink Book (<http://www.cdc.gov/vaccines/pubs/pinkbook/index.html>)
- the Yellow Book (<http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014>)
- chapters on the relevant diseases.

As not all diseases were included in these sources, the CDC search was extended with a search in the Morbidity and Mortality Weekly Reports (MMWR) archives for all diseases (<http://www.cdc.gov/mmwr/publications/index.html>). However, due to the large number of reports and time constraints this was not a fully comprehensive search.

The search on the WHO website was extended by searching for the diseases in this review combined with the terms incubation/shedding/excretion/excrete/exclusion.

- A Google search, using the following terms: incubation/shedding/excretion/excrete/exclusion/guideline.

## 2.3 Literature selection

### Selection procedure

References resulting from the search were selected by a three-phase selection procedure:

Screening of title and abstract (first selection phase): In this phase, titles of publications were first screened based on the inclusion and exclusion criteria. If the title was inconclusive, the abstract was read. References were divided into three categories: excluded, doubt and included. Articles with titles and abstracts that suggested that they contained information relevant to the research objective were included for full text assessment. Whenever it was clear that the article did not fulfil the eligibility criteria it was excluded. In case of doubt, the article was saved for the second selection step, i.e. both included and doubt articles were included in the second screening phase. References that were excluded during screening of title and abstract were stored in an indexed folder in Endnote.

**Screening of full article (second selection phase):** The articles selected during the first phase were assessed in full text. PDF-files of the original articles were downloaded and stored. Full texts were included if the reported information was relevant, based on the inclusion and exclusion criteria. The reasons for exclusion of full text papers were documented per article and summarised in an exclusion table.

**Screening during data-extraction phase:** further scrutiny of the article during the data-extraction phase could also lead to exclusion. For example, only in this phase does it sometimes become apparent that two papers based on the same dataset and presenting comparable outcomes have been included, and in that case one will be excluded.

The process of selection and exclusion of articles was registered in an Excel file and an Endnote library.

## Inclusion and exclusion criteria

The list of inclusion and exclusion criteria is presented in Table 2.1.

**Table 2.1. Inclusion and exclusion criteria**

Inclusion		Exclusion
Study subject	<ul style="list-style-type: none"> <li>Incubation, infectiousness/shedding and/or exclusion of child communicable disease</li> </ul>	<ul style="list-style-type: none"> <li>Other</li> </ul>
Study design	<ul style="list-style-type: none"> <li>Meta-analysis or systematic review</li> <li>Randomised controlled trials (RCTs)</li> <li>Non-randomised, prospective comparative studies of interventions</li> <li>Prospective, longitudinal, observational studies (where the measure of exposure occurred before the outcome), household studies</li> <li>Case-control studies, cross sectional studies, case-series</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies, in vitro studies, expert opinions, editorials, and letters to the editor</li> <li>Case studies</li> <li>Narrative reviews</li> <li>Modelling studies</li> </ul>
Study characteristics	<ul style="list-style-type: none"> <li>Study duration (no minimum)</li> <li>Number of subjects &gt;5</li> <li>Baseline data e.g. population characteristics available including at least age, sex, and type of setting</li> </ul>	<ul style="list-style-type: none"> <li>Other</li> </ul>
Population	<ul style="list-style-type: none"> <li>Healthy individuals of at least one month to 18 years, infected with a transmittable disease<sup>1</sup></li> <li>For objective 3: attending a school or other childcare setting</li> </ul>	<ul style="list-style-type: none"> <li>Immunocompromised/special needs/displaced populations</li> <li>NB: Data on adults<sup>1</sup></li> <li>NB: Use of medication (e.g., antivirals, chemoprophylaxis)<sup>1</sup></li> </ul>
Specific outcomes of interest	<ul style="list-style-type: none"> <li>For the most common transmittable childhood infectious diseases or those with a particular concern:               <ul style="list-style-type: none"> <li>Incubation period<sup>3</sup></li> <li>Period of infectiousness or duration of shedding</li> <li>Exclusion period</li> </ul> </li> </ul> <p>(At least one of the above; With clinical symptoms and caused by a defined infectious agent<sup>4</sup>)</p>	<ul style="list-style-type: none"> <li>Pandemic influenza</li> <li>Carriage<sup>2</sup></li> <li>Incidence of infectious disease</li> <li>NB: Asymptomatic infection<sup>1</sup></li> <li>NB: Breakthrough infection<sup>1, 5</sup></li> </ul>

<sup>1</sup>Focus was on data in children, who have symptomatic infections that are not breakthrough infections and who use no medication (unless standard practise). Studies in which part of the study population consisted of adults, had symptomatic or breakthrough infections, or used medication were eligible only if stratified data were available (children and adults; symptomatic and asymptomatic infections; yes and no breakthrough infection; yes and no medication;); with respect to treatment, the information for the treated stratum is also registered (for diseases that are usually treated).

<sup>2</sup>Prolonged (possibly years) excretion without symptoms. Information from acute symptomatic manifestation is eligible.

<sup>3</sup>In the extended review, the definition for this criterion was applied stringently; however, in the basic review some serial intervals (i.e. time from onset of symptoms in primary case to time of onset of symptoms in secondary case) were included as a proxy for incubation period if incubation period was not available.

<sup>4</sup>In some cases the infectious agent was not yet known, but the disease could be identified from the symptoms only (e.g. in the case of roseola infantum), and therefore these studies would be included.

<sup>5</sup>An infection by the same organism that a vaccine is designed to protect against; this may be caused by exposure to the organism before the vaccine took effect, or before the entire set of booster vaccines was administered.

## 2.4 Data extraction

Relevant data from papers that were considered pertinent were first extracted and inserted into data extraction forms in Excel format. This information was the basis for the extraction tables, see Chapter 3 and the extraction tables in a separate document on the ECDC website.

Organised by 1) disease group and 2) disease, this sheet contains information on:

Admin:	Extractor; objective (1, 2, 3); disease.
Reference:	Author; year; journal, aim, country; study design; study period and duration.
Population:	(Childcare) setting; source population or database; inclusion/exclusion criteria; sample description (size; age; gender).
Exposure:	Infectious agent, serotype; sampling specimens and frequency; laboratory testing methods.
Case info:	Case definition (text, including symptoms); case definition (category).
Outcome:	Definition of outcome (for each of the outcomes); incubation period; period of infectiousness; duration of shedding; exclusion period; effectiveness of exclusion period.
Comments:	Limitations of the study; other comments.

The following predefined rules were applied as much as possible during data-extraction:

- To describe the case definition both as text and as a categorical variable (clinical/laboratory/both/mixed)
- To describe in the definition of the exclusion period whether exclusion was based on the case definition and what the criteria for the end of exclusion were
- To extract incubation period, period of infectiousness, duration of shedding and exclusion period as the number of days from a defined point in time and until a defined point in time, unless the article states otherwise
- To extract measures of variation, if available
- To extract information on effectiveness of exclusion period as provided by the reference
- To extract data for each infectious agent separately, if more than one agent was involved.

## Assessment of quality aspects of individual articles

During literature selection, Pallas critically appraised the methodological quality of the articles that appeared to present relevant data for the review. This was done based on Evidence Based Medicine checklists, and aimed to identify quality limitations; these were then described in the extraction tables.

For this review, Pallas used the Coordination of Cancer Clinical Practice Guidelines (CoCanCPG, <http://www.cocancpg.eu/>), checklists which are available for different study designs, such as systematic reviews/meta-analyses, RCT's, cohort studies, and case-control studies. The CoCanCPG checklists, originally designed for developing cancer guidelines but also applicable to studies addressing other review questions including those regarding infectious diseases, combine the most important criteria on publication quality from the PRISMA (<http://www.prisma-statement.org/index.htm>) and STROBE guidelines (<http://www.strobe-statement.org/>).

Relevant publications in the field of infectious disease also include outbreak investigations, surveillance studies or other observational studies. Since for these types of studies no standard CoCanCPG checklists are available, Pallas adapted the existing CoCanCPG checklists to assess these types of studies for the existing review and also tailored them to the specific subject, for example by defining additional criteria, such as whether a measure of variation in the outcome of interest was provided.

The CoCanCPG checklists score qualitatively on predefined aspects of a study, using - - or -, 0, + or ++. The checklists are not designed to calculate a total quality score of summed + and - ,to assess differences in quality between studies.

## 2.5 Quality control

### Systematic review process

During the systematic review process, the following quality control measures were put in place:

- First screening phase: approximately 50% of titles and abstracts were screened in duplicate by two independent researchers from Pallas (disagreement <5%). The results were compared and discussed. The largest part of duplicate screening, in combination with discussion of any discrepancies, was performed directly at the start of the (first and extended) review, to achieve optimal alignment between reviewers during the rest of the screening process. When a researcher still doubted the relevance of a reference, it was included in the next screening phase, in order to limit the potential variation in selecting references between reviewers (see section 2.3).
- Second screening phase: approximately 25% of full text articles were critically appraised in duplicate by two independent researchers from Pallas. The results were compared and discussed early in this phase and in addition, all articles on which any doubts arose during the remainder of the screening phase were discussed within the team. For transparency, in case of exclusion the reason for exclusion was registered and summarised in a table.
- Data extraction: the evidence tables were compiled by two junior researchers, who fully (100%) cross-checked each other's work, and were reviewed for inconsistent or unclear content by the senior researcher of the project. All issues were discussed and considered within the team and this sometimes led to excluding initially included papers.
- Interpretation and presentation of the results: results of the review were discussed. Texts were written by junior and senior researchers, and reviewed and edited by the project leader of Pallas.

### Panel meetings

In November 2014, the findings of a first, more restricted, systematic literature search in PubMed were presented by Pallas during a meeting with an expert panel at ECDC premises. Feedback from the expert meeting was incorporated into the final report of this first review. In February 2015, the final report of this first review was presented by Pallas to the expert group by means of skype video. Feedback was incorporated in the protocol for extension of the review, leading to this report.

## 3. Review results

This systematic literature review has investigated two main sources of information:

- Peer-reviewed articles focusing on data in children, originating from
  - a systematic PubMed search
  - a systematic Embase search
  - a hand search of the identified articles, including reviews
- Other data sources, including grey literature and handbooks.

In this chapter, the results of the identification and selection process are described; in section 3.1, the peer-reviewed articles are addressed and in section 3.2 the other data sources. Information obtained from the included literature sources is presented in Chapter 5 (peer-reviewed articles) and Chapter 6 (other literature).

### 3.1 Screening and selection of peer-reviewed articles

#### Search in PubMed and Embase

The PubMed search yielded 9 129 references. The Embase search yielded 7 003 references, of which 3 488 were additional to the PubMed references. The screening and selection process is visualised in Figure 1 and described in further detail below.

The final search as presented in (which can be provided upon request) did not retrieve a set of 418 references that were retrieved and screened in the first review. This was due to minor changes in the terms of the final search. Of these, 16 were screened full text and found to be ineligible. The results have been added to the exclusion list.

#### Screening results

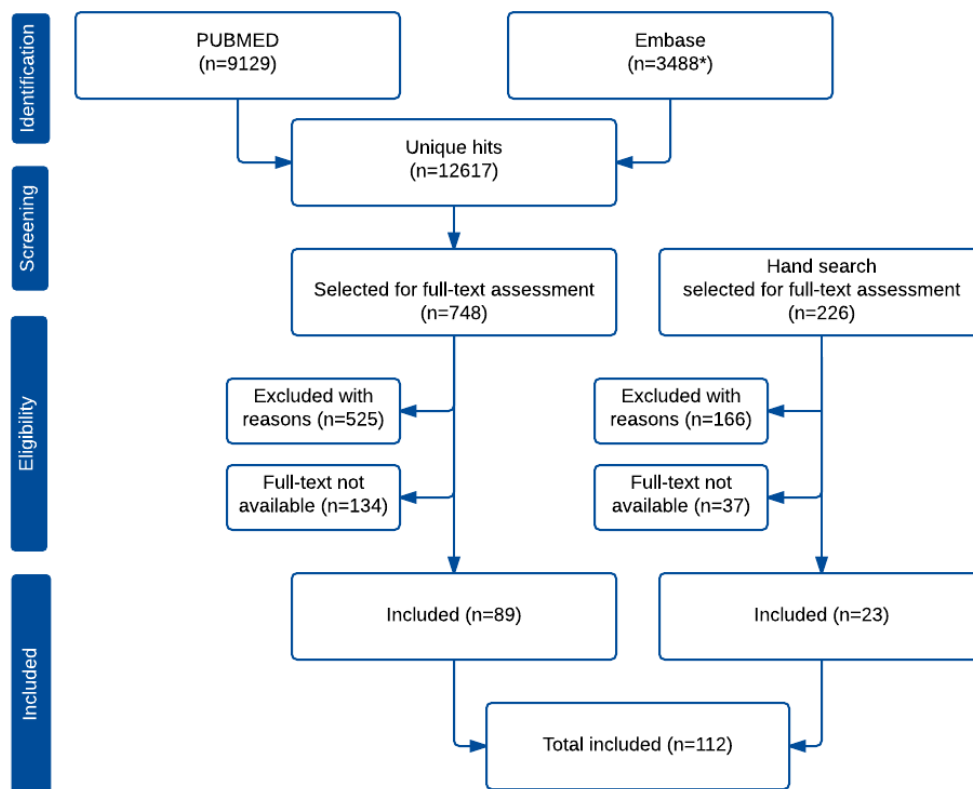
Based on title and abstract screening, a total of 748 references were selected. Main reasons for not selecting in this phase of screening were ineligible populations (e.g. neonates, adults) and ineligible outcomes (e.g. disease incidence, serotyping and vaccine-related outcomes). For the selected references, the full text was retrieved. A total of 134 references were not found and were thus not available for full text screening. For a large part, this was due to them being old publications in foreign languages and/or publication in national journals and also not available electronically.

After screening of the full articles, we excluded 525 articles. Reasons for exclusion in this phase of full text screening are presented for each reference separately in a separate document which can be requested. In total, 89 publications fitted the eligibility criteria.

Some of the excluded references were systematic reviews. These did not fit the eligibility criteria, e.g. because they did not present data for children specifically. The reference lists of all identified systematic reviews were screened for eligible individual studies and as such contributed to the hand search publications for our review. For one systematic review, addressing a similar review question as this review, the eligibility criteria could not be assessed, as population and study characteristics were not provided. Also, it stated to contain evidence that was not eligible for our review (opinions and clinical experience of experts not supported by published data and sample size  $\leq 5$ ). Therefore, it was decided to describe this reference under the 'Other data sources' section (Chapter 0).

#### Hand search

In total, 226 references were identified by hand search, of which 37 were not available for full text screening. After full text screening, 166 publications were excluded. Reasons for exclusion are presented for each reference separately in a separate document which can be provided upon request. A total of 23 publications from the hand search fitted our eligibility criteria.

**Figure 1. Flowchart of selection process**

\*Total Embase (n=7003) minus overlap in total PubMed

In total, 112 publications were included. The studies are described by disease group and disease in Chapter 4. Some studies addressed more than one disease/infectious agent, resulting in 119 summary tables.

Main reasons for exclusion were ineligible outcomes (e.g. serotyping, duration of symptoms), ineligible age (i.e. adults or newborns), and lack of stratified data (i.e. outcome combined for child/adult, symptomatic/asymptomatic, vaccinated/unvaccinated, treated/untreated groups).

## 3.2 Screening and selection results of other data sources

The findings of the grey and other literature search are addressed in Chapter 0. Apart from the systematic review, the information is mostly unsourced (i.e. no reference to studies underlying the information). However, these findings are described in this review as they concern key health organisations or reviewed handbooks.

### Websites of key health organisations

The guideline search showed that the CDC and WHO websites did not provide guidelines with evidence-based recommendations for exclusion period in school and other childcare settings, including overviews of sourced incubation periods and/or period of infectiousness for the combined infectious diseases in this review.

Further searching of the CDC website for the specific diseases resulted in relevant information from the Pink book, the Yellow book and MMWR. Some MMWR's also emerged from the PubMed search. As the amount of MMWR's is extensive but not easily searchable, this review could not cover the full scale of MMWR's. The WHO website also yielded information for specific diseases.



## Review and handbooks

As already mentioned in section 3.1, one systematic review was included as 'other data source'. Besides this, two other sources of information were included: one emerged from the PubMed search, i.e. 'Red Book' [113] and one was suggested by ECDC: 'managing disease in childcare and schools. A quick reference guide' [114]. The latter provides content from the Red Book and is also published by AAP. Therefore, results for the reference guide are only presented where it differs from the Red Book. It must be noted that a difference could be due to the Red Book being more recent.

## Google search

Several institutes and organisations provide easily accessible reports or factsheets with recommended exclusion period, mostly unsourced. Some examples are mentioned in Chapter 5.

## 3.3 Results peer-reviewed literature

In this chapter, key parameters extracted from pertinent references included in this review are summarised, organised by the five main categories of disease/agents. Tables summarising study characteristics and outcomes can be provided upon request.

For some publications in foreign languages not mastered by Pallas, data were entered by ECDC; as the information was not complete and Pallas was not able to screen and process it in the same manner as the other references in the review, the references have been excluded from the current review and the (limited) summary tables are available upon request.

## Vaccine preventable diseases

**Table 4.1. Included references for vaccine preventable diseases**

Disease/agent	References
Measles	Gahr 2014 [1], Lempriere 1931 [2], Parker 2006 [3], Paunio 1998 [4], Perucha 2006 [5], Shiraishi 1990 [6], Stillerman 1944 [7]
Meningococcal disease	-
Mumps	Brunell 1968 [8], Henle 1948 [9]
Pertussis	Kwantes 1983 [10], Stocks 1933 [11]
Rubella	Sever 1965 [12], Zhao 1992 [13]
Varicella	Asano 1985 [14], Gordon 1929 [15], Ma 2006 [16], Moore 1991 [17], Ozaki 1996 [18], Poulsen 2005 [19]

### Measles

Four studies included reporting on incubation period [2-5]; they generally range between 9 and 20 days, with a median value of around 13 days. Serial intervals in two studies [1, 7] ranged from 5–32 days, with a median value around 13 days. A median or range for period of infectiousness or duration of shedding was not found. However, virus was reported to be isolated from respiratory secretions from three days before onset of fever until 10 days after onset of fever and one day before onset of a rash until six days after onset of a rash [6]. Exclusion for contacts starting six days after exposure (and lasting 10 days) was not effective [2].

### Meningococcal disease

No eligible studies were identified.

### Mumps

One study reported an incubation period of 14–25 days (median 17 days) and period of shedding 0–3 days (median 0) after onset of symptoms [9]. Virus was isolated from pharyngeal swabs from 2 days before until 5 days after onset of parotitis [8]. For those patients with involvement of the salivary glands, virus could be isolated from saliva 2–6 days prior to onset of symptoms and up to 4 days after onset [9]. Exclusion at first sign of parotid swelling did not prevent spread in a children's tuberculosis ward [8].

### Pertussis

The incubation period of pertussis could be three days, but is probably about one week [11]; no maximum estimate is available from this reference. In a large monitoring study, shedding, measured as the isolation rate among all clinical cases over the study period, was 40% of patients at four weeks after illness onset, still 20% at six weeks and 10% at seven weeks after illness onset [10]. The authors speculate that due to the long duration of shedding for a relatively large group, exclusion from school for three weeks will not be effective [10]. It is advised when designing infection control measures to take into account possible contacts that are of pre-school age, for which the disease has more harmful consequences [11].



## Rubella

In the study by Zhao, the incubation period was reported to be 13–24 days (mean ~18 days) [13]. Virus was identified from throat swabs from 2–13 days before onset of a rash, with in a majority of cases at 5 days before a rash, until 2–6 days after the rash (when sampling was ended) [12].

## Varicella

No studies were identified reporting on the incubation period of varicella. However, three studies presented serial intervals for different settings, varying from 11–20 days with a mean/median around 14–16 days depending on type of contacts [14, 15, 19]. Regarding period of infectiousness, cases appeared not infectious 24 hours preceding eruption, but infectious before or five days after eruption; contact infection of chickenpox ceases about the end of the first week of the eruption or the beginning of the second [19]. This coincides with a study that found that cases were 3.6 (95% CI 2.4–5.4) times more likely to occur after exposure to a prodromal case child than at any other time [17], and a study that presented a period of shedding of 0–5 days (median 2 d) after appearance of a rash [18]. Exclusion from school for 7 days from onset of a rash or until all lesions were crusted (mean and median duration were 7 days) seemed not to have been effective in one study [17], but classes in which ill students remained in school longer than two days while ill with a rash had higher attack rates (40%–80%) compared to classes in which ill students were isolated immediately (<15%) [16].

## Food and waterborne diseases

**Table 4.2. Included references for food and waterborne diseases**

Disease/agent	References
<i>Viral gastrointestinal infections</i>	
Enterovirus infections (non-polio, non-hand-foot-and-mouth)	Begier 2008 [20]
Viral Gastroenteritis by	
Adenovirus	Uhnnoo 1984 [21], Van 1992 [22]
Astrovirus	Cruz 1992 [23], Esahli 1991 [24], Mitchel 1993 [25]
Noro-/calicci-/sapovirus	Barrabeig 2010 [26], Godoy 2005 [27], Guest 1987 [28], Grohmann 1991 [29], Hoebe 2004 [30], Kappus 1982 [31], Kirkwood 2008 [32], Marks 2003 [33], Murata 2007 [34], Rockx 2002 [35], Saito 2014 [36], Struve 1994 [37], Usuku 2008 [38]
Rotavirus	Davidson 1975 [39], Gaggero 1992 [40], Guarino 1994 [41], Hilpert 1987 [42], Mukhopadhyaya 2013 [43], Pickering 1988 [44], Rahman 2012 [45], Richardson 1998 [46], Rosenfeldt 2002 [47], Sarker 1998 [48], Stals 1984 [49], Uhnnoo 1986 [50]
<i>Other viral infections</i>	
Hepatitis A	Brodribb 1952 [51], Krugman 1967 [52], Reid 1986 [53]
<i>Bacterial infections</i>	
Campylobacteriosis	Evans 1996 [54], Korlath 1958 [55], Mizuno 1985 [56], Pai 1983 [57], Salazar-Lindo 1986 [58], Taylor 1988 [59], Uhnnoo 1986 [50], Wood 1992 [60]
<i>Escherichia coli</i> infections	Al-Jader 1999 [61], Belongia 1993 [62], Brandt 1994 [63], Brown 2012 [64], Dabke 2014 [65], Haltalin 1972 [66], Karch 1995 [67], Keene 1994 [68], MacDonald 2014 [69], Shah 1996 [70], Uhnnoo 1986 [50], Vonberg 2013 [71]
Salmonellosis (non-typhoid)	Abe 2004 [72], Balfour 1999 [73], Barbara 2000 [74], Cowden 1989 [75], El-Radhi 1992 [76], Huang 2012 [77], Kazemi 1973 [78], Lennox 1954 [79], Matsui 2004 [80], Nelson 1980 [81], Raguenaud 2012 [82], Sheu 1990 [83]
Typhoid fever	Anita 2012 [84], Galloway 1986 [85], Taylor 1974 [86], Usera 1993 [87]
Paratyphoid fever	-
Shigellosis	Haltalin 1967 [88], Haltalin 1972 [66], Keene 1994 [68], MacIntubee 1987 [89], Tauxe 1986 [90]
<i>Parasitic infections</i>	
Giardiasis	Bartlett 1991 [91]

## Enterovirus infections (non-polio, non-hand-foot and mouth)

One study was included on echo- and coxsackievirus. It reported exposure of cases four days before the primary illness peak [20].

## Gastroenteritis by Adenovirus

No studies were identified reporting on incubation period or period of infectiousness of adenovirus. Excretion was found to take place up to 8–23 days (8–13 in 9/10 patients) after onset of disease [21]. One study found virus excretion as from seven days prior to diarrhea to 11 days after diarrhea stopped; mean duration of total excretion (i.e. including time before onset of symptoms) was  $4.2 \pm 0.4$  [22]. No information was found on exclusion periods.

### ***Gastroenteritis by Astrovirus***

Although no studies were found presenting incubation periods for Astrovirus, one study found a serial interval of 2–13 days (mean: 3 days) [24]. The same study reported a period of shedding ranging from 1–10 days after onset of diarrhea (median: 3.5 days). The time span during which shedding took place was from maximally two weeks before diarrhea up to 20 days after diarrhea had ceased [23, 25] with a duration including time before onset of symptoms ranging from 2–30 days (median 8.5 days) [25, 39].

### ***Gastroenteritis by Noro-/calici-/sapovirus***

For Norovirus, incubation periods in different settings were reported ranging from 7–72 hours [26, 27, 29, 30]. Period of shedding ranged from 2–47 days after disease onset (median depending of age, ranging among studies from 10 days in general up to 42 days among those <6 months of age) [32, 34, 36].

For Norwalk or Norwalk-like virus, an incubation period was found of 0–2 days (median: approximately 1 day) [70, 49]. Shedding up to 22 days has been observed for ~25% of cases in the study by Rockx [35], and shedding duration differed by age (On day 22, 35% of those <1 y and 0% of those ≥12 y was found positive). Exclusion by school closure for four days, from day 18–21 after onset of the outbreak (including cleaning using chlorine-based agents appeared to be effective [33].

For Calicivirus, no publications were found reporting on incubation period. Shedding duration was 0–12 days from onset of diarrhea [37]. The time span during which shedding took place was at least one day before until >7 days after the onset of illness [65]. Exclusion of ill children from daycare centres until 24 hours after last episode of gastroenteritis and the subsequent closure of daycare centres for 11 days (with additional hygiene measures) appeared not effective [29].

For Sapovirus, the incubation period ranged from 0–6 days (median: 2.5 days) [38]. Shedding was found up to day 15 after onset of symptoms [35].

### ***Gastroenteritis by Rotavirus***

For Rotavirus, an incubation period was reported of less than 48 hours in one study [39]. No data were found on the period of infectiousness of rotavirus cases. However, period of shedding was reported in 12 studies, and varied depending on definition: among the studies measuring from the moment of hospital admission, shedding ranged from 2 to 8 days, with reported medians of approximately 3.5–6 days [39, 42, 45]. Studies measuring from onset of symptoms/diarrhoea, reported shedding of four days up to 57 days, with medians among studies of 7.5–4 days [41, 43, 46, 49, 50]. In one of these studies [49], shedding stopped at the maximum 2–3 days after cessation of diarrhoea. One study measured from detection in stool, with diagnosis both on admission and nosocomially acquired; shedding ranged 1–5 d, mean 2.5 days [40]. One study measured on the day before or after cessation of diarrhoea; 50% of tested children, tested positive the day before diarrhoea; shedding lasted up to 34 days [44]. Two studies reported shedding from study enrolment of subjects, ranging from 1–<5 days [15], and a mean of 2.9 days [48].

### ***Hepatitis A***

For Hepatitis A, an incubation period of 30–125 days (median 37 days) was reported, based on serum levels [52]. Another study reported a serial interval with a smaller range of 20 up to 32 days, with a median of 27 days [51]. No data were found on period of infectiousness or shedding of Hepatitis A cases. Exclusion from school until clinical recovery (combined with hygiene measures) were apparently successful [53].

### ***Campylobacteriosis***

For *Campylobacter jejuni*, reported incubation periods in three studies ranged from 1–10 days, with median of around three days [63, 120, 133]. No studies reported on the period of infectiousness of cases. The period of shedding that was observed for *Campylobacter jejuni* or *coli* depended largely on the moment that measuring started, e.g. at study start (1–38 days, mean ± SD, 16.8 ± 12.5; [57], at onset of diarrhoea (6–90 days, mean: 30; median: < 21 [50] and up to 6 weeks [55]), at start of treatment (0–5 days, mean ± SE: 2.2 ± 0.6; [58] or at first visit to clinic (1–8 weeks, mean ± SEM in those <1 yr: 14 days ± 2, in those 1–5 yrs: 8 days ± 2; [59]. Mean shedding appeared lower in antibody positive cases than in antibody negative cases [56].

### ***Escherichia coli (E.coli) infections***

#### ***Enterohemorrhagic or shiga-toxin/verocytotoxin producing E. coli 0157***

For EHEC/STEC/VTEC O157, incubation periods were reported in the range of 1–21 days (median 4–4.5 days) [63, 68]. No data were found for period of infectiousness of cases. Four studies presented periods of shedding, within the range of 2–62 days after onset of illness (diarrhea or hemorrhagic colitis) [62, 65, 67, 70]. Two of these studies reported means/medians around 30 days [65, 70], in two studies the mean/median period of shedding was lower, with 13 and 17 days, respectively [62]. The period of shedding in HUS cases appeared to be longer, between 5–124 days after onset of diarrhea (mean/median 21 days, [67].

Exclusion of all children from a nursery until they have two negative faecal stools appeared to be effective in ending an outbreak [61]. The duration of exclusion from childcare facilities ranged from 28–52 days (median 39.5 days; in almost a quarter of the cases of which both duration of shedding and exclusion were known, exclusion periods were  $\geq 2$  weeks longer than the duration of shedding [65].

### **Other enterohemorrhagic (EHEC) or shiga-toxin/verocytotoxin producing *E. coli* (STEC/VTEC)**

For other EHEC, STEC or VTEC, no incubation periods or periods of infectiousness were found in literature. Reported periods of shedding were within the range of 5 up to 98 days [64–66, 69, 71]. Two studies reported a median duration of around 31 days after onset of illness [64, 65]. In one study, the median (95% CI) shedding duration for children aged  $<15$  with HUS (27.5 (CI 17.2–41.3) days from onset of illness) was lower than for those with no HUS (52.3 (38.5–68.8) days) [71]. As for O157, also for other EHEC/STEC/VTEC the exclusion of all children from childcare centre until two consecutive negative stools ( $\geq 48$  hours apart) seemed effective [64]. School closure for five days, combined with exclusion of confirmed cases until they had three or five consecutive negative cultures (depending on severity of cases) showed an exclusion duration ranging from 37–109 days (median: 71 days) that resulted in interruption of the outbreak [69].

### **Enteropathogenic *E. coli* (EPEC)**

For EPEC, no incubation periods and periods of infectiousness of cases were reported in literature. The observed period of shedding of cases ranged from 20–36 days after onset of diarrhea (mean: 29 days) [50]. No information on exclusion interventions was available.

## ***Salmonella* infections**

### **Salmonellosis (non-typhoid)**

Regarding the several serotypes of *Salmonella*, reported incubation periods varied between studies from  $<24$  hours to a maximum 16 days, with medians between 1–8 days depending on serotype and setting [72, 75, 80, 82]. No data on period of infectiousness were found. Period of shedding of one day up to 22 weeks from exposure or infection has been reported (refs [73, 74, 79, 81]. Within this range were also the periods of shedding measured from first positive sample [83], or from admission to hospital [76, 77]. No studies on exclusion interventions were detected.

### **Typhoid fever**

For *Salmonella* Typhi, incubation periods were reported in three studies, ranging between 4–34 days (medians 14–19 days, [84–86]. No data were found on period of infectiousness of typhoid fever cases. One study reported that all stool samples of cases were negative four months after being clinically cured [87].

### **Paratyphoid fever**

No eligible studies were identified.

## ***Shigella* infections**

For various species of *Shigella*, the observed incubation period in two studies was 1–6 days, with mean/median of approximately two days [68, 89]. No data were found for the period of infectiousness of cases, but period of shedding was found to be between 1–10 days from the start of therapy/study [66, 88]. Transmission ceased within two days [90] after exclusion of cases and return to the daycare centre with appropriate antimicrobial therapy after diarrhoea had ceased, and subsequent isolation in a separate room until two negative successive stool cultures, or closure of the daycare centre until cases had 2 negative successive negative stool cultures after antimicrobial therapy,

## ***Giardia* infections**

No studies were found reporting on incubation period, period of infectiousness or shedding. When comparing three control strategies regarding exclusion, at the end of the six-month follow-up period, no exclusion strategy was associated with significantly lower prevalence of *Giardia*, although the six-month prevalence in all three groups was significantly lower than the prevalence at the time of intervention [91].

## Airborne diseases

**Table 4.3. Included references for airborne diseases**

Disease/agent	References
Influenza	Brocklebank 1972 [92], Frank 1981 [93], Hall 1975 [94], Hall 1978 [95], Hall 1979 [96], Jackson 2013 [97], Sato 2005 [98], Sugisaki 2013 [99]
Streptococcal infections	
-Scarlet fever	Lamden 2010 [100], Hoek 2006 [101]
-Streptococcal pharyngitis	Snellman 1993 [102]
-Streptococcal impetigo	-
Respiratory tract infections with RSV	Frank 1981 [93], Hall 1976 [103], Hall 1976 [104], Hall 1978 [105], Okiro 2010 [106], Sterner 1966 [107], Sung 1993 [108], von Linstow 2006 [109]
Infectious mononucleosis	Sumaya 1985 [110]

### *Influenza*

No studies were identified reporting on the incubation period or period of infectiousness for influenza. Five studies reported on influenza A shedding, measured from onset of illness and/or hospital admission [92-95, 98]. The virus could be isolated as early as eight days before onset of symptoms and up to 21 days; a mean of around seven days was reported in one study [98]. Influenza B virus shedding was measured from onset of illness in three studies [93, 96, 98]. Virus could be isolated up to 15 days (and not before onset); a mean of around six days (measured by viral culture) and 4.6 days (measured by antigen detection) was reported in one study [98]. Studies reporting on exclusion of cases were not identified; However, school closure [97] and class closure [99] may be effective in controlling outbreaks of seasonal influenza, depending on the timing of the intervention and the measure of effectiveness.

### *Streptococcal infections*

#### *Scarlet fever*

No studies were identified reporting on the incubation period or period of infectiousness/shedding of scarlet fever. Two studies reported on period of exclusion [100, 101]. In one investigation, exclusion of symptomatic children from a daycare centre, in combination with treatment with penicillin, and subsequent closure of the centre resulted in ending an outbreak [101]; in the other study, exclusion of symptomatic cases from school until they had received 24 hrs of penicillin treatment (which was often <24 hrs in practice) was not effective in ending an outbreak [100].

#### *Streptococcal pharyngitis*

No studies were identified reporting on the incubation period or period of infectiousness/shedding of streptococcal pharyngitis. One study covered the period of exclusion (in combination with treatment); even when asymptomatic, 37% of pharyngitis cases still had positive throat culture the morning after starting antibiotic therapy and it is advised to complete a full 24 hrs of antibiotic therapy [102].

#### *Streptococcal impetigo*

No eligible studies were identified.

### *Respiratory tract infections with RSV*

No studies were identified reporting on the incubation period or the exclusion period of respiratory syncytial virus. Seven studies reported on shedding [93, 103-109]. RSV was isolated up to four days before symptom onset [93] and shedding continued up to 27 days.

### *Infectious mononucleosis*

No studies were identified reporting on the incubation period or the exclusion period of infectious mononucleosis. In one study, duration of shedding was reported to continue more than 29 weeks; 50% of the total sample shed for at least 9–28 weeks [110].

## Other transmissible diseases common among children

**Table 4.4. Included references for other transmissible diseases of interest in pediatrics**

Disease/agent	References
Roseola infantum (Exanthem subitum)	Barenberg 1937 [111], Suga 1998 [112]
Fifth disease (Erythema infectiosum, Parvovirus infection)	-
Staphylococcal impetigo	-
Hospital colonisation by resistant pathogens	-
MRSA infections	-

### *Roseola infantum (Exanthem subitum)*

One study reported an incubation period approximated by a serial interval of 5–15 days (mean 10 days) [111]. Another study reported (intermittent) shedding in saliva and stool for 60–90 days [112].

### *Fifth disease (Erythema infectiosum, Parvovirus infection)*

No eligible studies were identified.

### *Staphylococcal impetigo*

No eligible studies were identified.

### *Hospital colonisation by resistant pathogens*

No eligible studies were identified.

### *MRSA infections*

No eligible studies were identified.

## Summary table

Table 4.5 presents the main relevant parameters from the studies included in this review, representing its objectives 1, 2 and 3, i.e. incubation period, period of infectiousness/shedding and exclusion period.

The following comments or restrictions apply to this table:

- Column incubation period: the incubation period (time from exposure to onset of symptoms) is provided as a range, unless otherwise indicated. In the first part of the review, if no incubation period was available but in some cases a serial interval (time from onset of symptom in primary case to onset of symptoms in secondary case) was given, the latter was extracted and labelled as such, and used as a proxy for the incubation period.
- Column period of shedding: this was given as a range indicating the number of days to the end of shedding, ideally starting from onset of symptoms, unless otherwise indicated.
  - Time span during which shedding took places indicates time period from the first measured positive sample to the last measured positive sample in the study population (not necessarily duration in a single person or summary of durations in individuals), within the window of measurement.
- Exclusion period: data on exclusion period varied greatly between studies, ideally the exclusion period was given and whether or not it was successful in preventing spread of the infection (mentioning the setting)

**Table 4.5 Overview of relevant outcomes from all included peer-reviewed studies.**

Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
<b>Vaccine preventable diseases</b>						
Measles		10–20 d (mean: 16 d; median 17 d) <sup>a</sup> ; 9–14 d (median: 12 d) <sup>b</sup> ; 9–18 d (mean: 13.8 d) <sup>c</sup> ; 9–16 d (mean: 12.1 d; median: 13 d) <sup>g</sup> <u>Serial intervals:</u> 5–32 d (median: 13.5 d) <sup>d</sup> ; 8–19 d (mean: 12.4 d) <sup>e</sup>		<u>Time span during which shedding took place:</u> Measles virus isolated in respiratory secretions - 3 d after onset of fever to 10 d after onset of fever <sup>f</sup> ; - 1 d before onset of a rash to 6 d after onset of a rash <sup>f</sup>	Exclusion of known susceptible contacts from a boarding school for 10 d (from 6–16 d after exposure) did not prevent spread of infection <sup>a</sup>	<sup>a</sup> Lempriere 1931[2] <sup>b</sup> Paunio 1998[4] <sup>c</sup> Perucha 2006[5] <sup>d</sup> Gahr 2014[1] <sup>e</sup> Stillerman 1944[7] <sup>f</sup> Shiraishi[6] <sup>g</sup> Parker 2006[3]
Meningococcal disease						-
Mumps	strains F and B <sup>a</sup> ; majority D6 <sup>b</sup>	14–25 d (median: 17 d; mean: 18 d) <sup>a</sup>		0–3 d (median 0 d) after onset of symptoms <sup>a</sup> <u>Time span during which shedding took place:</u> Mumps virus was isolated in pharyngeal swabs 2 d before the onset of parotitis up to 5 d after the onset of parotitis <sup>b</sup> ; Mumps virus was isolated in mouthwashings 10 d before onset of symptoms up to 4 d after onset of symptoms <sup>a</sup>	Isolation at first sign of parotid swelling did not prevent spread in children's tuberculosis ward <sup>b</sup>	<sup>a</sup> Henle 1948[9] <sup>b</sup> Brunell 1968[8]
Pertussis	<i>Haemophilus pertussis</i> <sup>a</sup> ; <i>Bordetella pertussis</i> <sup>b</sup>	Within the same household: 3 d, most probably 7 d; unknown upper limit <sup>a</sup>		~40% of patients at 4 weeks and ~20% at 6 weeks and ~10% at 7 weeks after illness onset <sup>b</sup>	Expected by authors, not directly tested: Exclusion for 3 weeks from school from onset of paroxysmal cough is not likely to have any significant effect as for a large group shedding is longer <sup>b</sup> ; Expected by authors, not directly tested: Keep infected children at school until the first sign of catarrh or cough, to protect younger children <sup>a</sup>	<sup>a</sup> Stocks 1933[11] <sup>b</sup> Kwantes 1983[10]
Rubella		13–24 d (mean: 17.8 d) <sup>a</sup>		<u>Time span during which shedding took place:</u> In patients with both a rash and enlarged lymph nodes, virus isolated in samples as early as 13 ds before onset of a rash; 5 ds before a rash in the majority of cases; 2 d before the rash in all cases; virus persisted for at least 2 d following a rash; and up to 6 d after onset of a rash (end of sampling) <sup>b</sup>		<sup>a</sup> Zhao 1992[13] <sup>b</sup> Sever 1965[12]

Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
Varicella		Serial intervals/Incubation period: Among family contacts: 13–18 d (mean $\pm$ SD: 14.0 $\pm$ 1.4 d) <sup>a</sup> ; Serial intervals: Among patients in scarlet fever ward: 11–20 d (median: 15 d) <sup>b</sup> Mean: 15.2 d (95% CI 14.6–15.7) for exposure in same bed; 15.9 d (95% CI 15.2–16.6) for exposure in same room; 16.1 (95% CI 15.4–16.9) for exposure in same household; 16.5 d (95% CI 16.0–17.1) for cases exposed from another household <sup>c</sup>	Not infectious 24 hours preceding the eruption. Possible that contact infection of chickenpox ceases about the end of the first week of the eruption or the beginning of the second. Varicella certainly is infectious by contact on or before the 5th d <sup>c</sup>  Cases were 3.6 (95% CI 2.4–5.4) times more likely to occur after exposure to a prodromal case child than at any other time (e.g. after classmates returned after having varicella). <sup>d</sup>	0–5 d (median: 2 d) after appearance of a rash <sup>e</sup>	Exclusion from school for 7 d from onset of a rash or until all lesions were crusted (mean and median duration were 7 d) seemed not to have been effective: most transmission already occurred after exposure to prodromal cases <sup>d</sup> ; Classes in which ill students remained in school >2 d while ill with a rash had higher attack rates (40%–80%) compared to classes in which ill students were isolated immediately (<15%). Also secondary attack rates were higher, RR=10 (CI 3.7–29.0) <sup>f</sup>	<sup>a</sup> Asano[14] <sup>b</sup> Gordon[15] <sup>c</sup> Poulsen[19] <sup>d</sup> Moore[17] <sup>e</sup> Ozaki 1996[18] <sup>f</sup> Ma 2006[16]
<b>Food and waterborne diseases</b>						
<b>Viral gastrointestinal infections</b>						
Enterovirus infections (non-polio, non-hand-foot and mouth)	Echovirus 30 and Coxsackievirus <sup>a</sup>	Exposure 4 d before primary illness peak <sup>a</sup>				<sup>a</sup> Begier 2008[20]
Gastroenteritis by adenovirus	Enteric Adenovirus 40 and 41 <sup>a,b</sup>			Excretion up to 8–23 d after onset of disease <sup>a</sup> Time span during which shedding took place: Virus was excreted from 7 d prior to diarrhea to 11 d after diarrhea stopped. Mean duration of total excretion (i.e. including time before onset of symptoms): 4.2 $\pm$ 0.4 d <sup>b</sup>		<sup>a</sup> Uhnnoo 1984[21] <sup>b</sup> Van 1992[22]
Gastroenteritis by astrovirus		Serial interval: 2 –13 d (mean: 3 d) <sup>a</sup>		*Among all symptomatic cases (n=18): range: 1–10 d after onset of diarrhea, median: 3.5 d after onset of diarrhea <sup>a</sup> Time span during which shedding took place: Virus was excreted from 8 d before diarrhea to 20 d after diarrhea had ceased. Mean duration of total excretion (i.e. including time before onset of symptoms): range: 2–30 d; median 8.5 d <sup>b</sup> Astrovirus was measured from 2 weeks before onset of diarrhea and detected during this period; for $\geq$ 22 days into the diarrhea episode; and measured up to 7 days after episodes were over, and detected during this period. <sup>c</sup>		<sup>a</sup> Esahli 1991[24] <sup>b</sup> Mitchell 1993[25] <sup>c</sup> Cruz 2012 [23]



Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
Gastroenteritis by calicivirus/norovirus	Calicivirus <sup>j,l</sup> ; Norovirus <sup>d,h</sup> ; Norovirus genotype Birmingham <sup>a</sup> ; Norovirus GI and GII <sup>k</sup> ; Norovirus GGII.2 <sup>c</sup> ; Norovirus GII.4 and GII.6 <sup>g</sup> ; Norwalk virus <sup>b,e</sup> ; Norwalk-like virus <sup>f,i</sup> ; Sapporo-like virus <sup>l</sup> ; sapovirus <sup>m</sup>	Norovirus 7–72 hours (mean: 30 hours) <sup>a</sup> ; 24–44.5 hours (mean: 32 hours) <sup>c</sup> ; 24–26 hours <sup>l</sup> ; 19–51 hours (median: 25.0 hours) <sup>d</sup> ; Norwalk or Norwalk-like virus 0–2 d (median: 1 d) <sup>b</sup> ; 0–45 hours (mean: 26 hours) <sup>e</sup> ; median: 1 d; mean (± SD): 1.5 (± 1.1) d <sup>f</sup> ; Sapovirus 0–6 d (median: 2.5 d) <sup>m</sup>		Calicivirus 0–12 d from onset of diarrhoea <sup>j</sup>  Norovirus 2–38 after disease onset (median: 11.5 d) <sup>g</sup> ; 5–>47 (median among those ≤6 months: 42 d; among those >1 yr: 10 d) <sup>h</sup> ; Median: 31.5 d <sup>k</sup> Norwalk-like virus 78%, 43%, 34%, 26% of isolates were positive on d 1, 8, 15 and 22 after onset of symptoms, respectively <sup>l</sup> Sapporo-like virus 89%, 58%, 14% and 0% of isolates were positive on d 1, 8, 15 and 22, respectively, after onset of symptoms <sup>i</sup> Time span during which shedding took place: Calicivirus was excreted from at least 1 day before until >7 days after the onset of illness <sup>l</sup>	Calicivirus Ill children excluded from daycare centre until 24 hours after last episode of gastroenteritis and closure of daycare centre for 11 ds (and additional hygiene measures). The outbreak subsided after 11 weeks, apparently independently of all the public health measures that had been taken. <sup>l</sup> Norwalk-like virus School closure for 4 ds, from d 18 - 21 of outbreak (including cleaning using chlorine-based agents). Outbreak stopped. <sup>f</sup>	<sup>a</sup> Hoebe 2004[30] <sup>b</sup> Kappus 1982[31] <sup>c</sup> Barrabeig 2010[26] <sup>d</sup> Godoy 2005[27] <sup>e</sup> Guest 1987[28] <sup>f</sup> Marks 2003[33] <sup>g</sup> Kirkwood 2008[32] <sup>h</sup> Murata 2007[34] <sup>i</sup> Rockx 2002[35] <sup>j</sup> Struve 1994[37] <sup>k</sup> Saito 2014[36] <sup>l</sup> Grohmann 1991[29] <sup>m</sup> Usuku 2008[38]
Gastroenteritis by rotavirus	Type G and P <sup>b</sup> ; G2P4, GIP8 and G9PUT <sup>9</sup>	<48 hours <sup>a</sup>		2–8 d from hospital admission (median: 6 d) <sup>a</sup> ; 4–57 d after onset of diarrhea (median:10 d) <sup>b</sup> ; Up to 30 d after onset of symptoms <sup>c</sup> ; 1–5 d ( median: 2d; mean: 2.5 d) <sup>d</sup> ; Mean (95% CI) 179 (162.7–195.3) hours from first loose stool <sup>e</sup> ; Mean (± SE:) duration of shedding from admission to the hospital 1982–1983: 3.91 d (± 0.51) 1983–1984: 3.58 d (± 0.48) 1984–1986: 5.02 d (± 0.29) <sup>f</sup> ; 14–51 d from onset of symptoms; (median: 24 d; IQR: 22–31 d) <sup>g</sup> ; 100%, 100%, 88%, 25%, 20%, 25% shed rotavirus on d 1, 2, 3, 5, 7, 8 from admission to hospital <sup>h</sup> ; 100%, 81%, 69%, 56%, 46% on d 1, 2, 3, 4, 5, respectively, from inclusion in study <sup>i</sup> ; Mean 2.9 d from study enrollment <sup>j</sup> ; Shedding during the 7 d after onset of diarrhea: 84%; shedding throughout the period of diarrhea: 68%; shedding stopped 2–3 d after the cessation of diarrhea <sup>k</sup> Some shedding up to 13 days before diarrhea (50% of tested sample 1 day before diarrhea); and up to 34 days after diarrhea (~50% of tested sample up to day 3) <sup>l</sup>		<sup>a</sup> Davidson 1975[39] <sup>b</sup> Richardson 1998[46] <sup>c</sup> Uhnnoo 1986[50] <sup>d</sup> Gaggero 1992[40] <sup>e</sup> Guarino 1994[41] <sup>f</sup> Hilpert 1987[42] <sup>g</sup> Mukhopadhyaya 2013[43] <sup>h</sup> Rahman 2012[45] <sup>i</sup> Rosenfeldt 2002[47] <sup>j</sup> Sarker 1998[48] <sup>k</sup> Stals 1984[49] <sup>l</sup> Pickering 1988[44]
<b>Other viral infections</b>						
Hepatitis A		30–125 d (median: 37 d) (based on abnormal serum transaminase level) <sup>a</sup>  Serial interval: 20–32 d (median: 27 d) <sup>b</sup>			Exclusion from school until clinical recovery (and hygiene measures). These measures were apparently successful because no further cases occurred in either school after the lapse of one incubation period from the date the measures were instituted. <sup>c</sup>	<sup>a</sup> Krugman 1967[52] <sup>b</sup> Brodribb 1952[51] <sup>c</sup> Reid 1986[53]



Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
<b>Bacterial infections</b>						
Campylobacteriosis	<i>C. jejuni</i> <sup>a, b, c, d, e, f, h</sup> ; <i>C. jejuni</i> and <i>C. coli</i> <sup>g</sup>	2–7 d (median: 4 d) <sup>a</sup> 1–10 d (median: 3 d) <sup>b</sup> 24–128 hrs (median 66, mean 68) <sup>h</sup>		1–38 d from study start (mean ± SD, 16.8 ± 12.5) <sup>c</sup> ; 6–90 d after onset of diarrhea (mean: 30 d; median: < 21 d) <sup>d</sup> ; Mean in those who were antibody positive: 5.9 ± 1.6 d and antibody negative: 13.8 ± 4.6 d (unclear when started) <sup>e</sup> ; 0–5 d from start of treatment; mean ± SE: 2.2 ± 0.6 d <sup>f</sup> ; 1–8 weeks from first visit to clinic; mean ± SEM in those <1 yr: 14 d ± 2, in those 1–5 yrs: 8 ± 2 d <sup>g</sup> Up to 4 weeks (6 weeks for n=1) from onset of symptoms <sup>h</sup>		<sup>a</sup> Evans 1996[54] <sup>b</sup> Wood 1992[60] <sup>c</sup> Pai 1983[57] <sup>d</sup> Uhnoo 1986[50] <sup>e</sup> Mizuno 1985[56] <sup>f</sup> Salazar-Lindo 1986[58] <sup>g</sup> Taylor 1988[59] <sup>h</sup> Koriath [55]
<b>Escherichia coli infections</b>						
<i>E. coli</i> O157:	O157 <sup>f</sup> ; O157:H7 <sup>a, b, e, h</sup> ; VTEC O157 (phage type 2) <sup>i</sup> ; VTEC O157 and O26 (phage types 21/28, 8 and 2) <sup>d</sup>	1–10 d (median 4 d) <sup>a</sup> ; <1–21 d (median: 4.5 d) <sup>b</sup>		Median: 31 d after onset of illness (IQR 17–41 d) <sup>d</sup> ; 2–62 d from diarrhea onset (median: 17 d) <sup>e</sup> ; Diarrhea or hemorrhagic colitis: 2–62 d after onset of diarrhea (mean or median: 13 d) <sup>f</sup> ; HUS: 5–124 d after onset of diarrhea (mean or median: 21 d) <sup>f</sup> ; Mean ± SD: 30.1 ± 13.0 d after onset of diarrhea <sup>h</sup> ;	All children excluded from nursery until 2 negative faecal stools; effective in ending outbreak <sup>i</sup> ; All children excluded from childcare centre until 2 negative consecutive stools (≥48 hours apart); no evidence of continued transmission <sup>e</sup> ; Median duration of exclusion from childcare facilities 39.5 d (IQR 28–52 d); exclusion period ≥2 weeks longer than the duration of shedding in 34/150 cases (23% (95%CI 16–30) where both duration of shedding and exclusion were known <sup>d</sup> ;	<sup>a</sup> Keene 1994[68] <sup>b</sup> Brandt 1994 [63] <sup>d</sup> Dabke 2014[65] <sup>e</sup> Belongia 1993[62] <sup>f</sup> Karch 1995[67] <sup>h</sup> Shah 1996[70] <sup>i</sup> Al-Jader 1999[61]
Other enterohemorrhagic <i>E. coli</i> (EHEC) or STEC/VTEC:	O26:H11 <sup>c</sup> ; STEC O104:H4 <sup>i</sup> ; STEC O103:H2 <sup>k</sup> ; O26 (phage types 21/28, 8 and 2) <sup>d</sup> O111, O119, O55, O126, O127, O128 and O86 <sup>j</sup>			14–52 d after onset of illness (median: 30.5 d) <sup>c</sup> ; Median (95% CI) for those aged <15 and HUS: 27.5 (CI 17.2–41.3) d from onset <sup>i</sup> ; for those aged <15 and no HUS: 52.3 (38.5–68.8) d <sup>i</sup> ; Time to negative culture >48 hours after start of study: 8/11 (73%); Culture positive after 5 d after start of study: 6/10 (60%) <sup>j</sup> ; 7–98 d from onset of symptoms <sup>k</sup>	School closed and reopened 5 d later for children with 5 consecutive negative results (diagnosed with stx2-positive STEC or an STEC serogroup; uncomplicated diarrhea with only stx1-positive STEC but serotype previously associated with HUS; or STEC infection with severe clinical presentation, such as bloody diarrhoea or HUS) or 3 consecutive negative results (uncomplicated diarrhea with only stx1-positive STEC). Duration of exclusion for confirmed cases (n=6, including one asymptomatic case) (range 37 - 109 d; median: 71 d). The outbreak was interrupted <sup>k</sup>	<sup>c</sup> Brown 2012[64] <sup>i</sup> Vonberg 2013[71] <sup>j</sup> Haltalin 1972[66] <sup>k</sup> MacDonald 2014[69]
Enteropathogenic <i>E. coli</i> <sup>g</sup> ;				20–36 d after onset of diarrhea (mean: 29 d) <sup>g</sup> ;		<sup>g</sup> Uhnoo 1986[50]

Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
<b>Salmonella infections</b>						
Salmonellosis (non-typhoid)	<i>S. Enteritidis</i> <sup>a,h</sup> ; <i>S. Enteritidis</i> PT1 <sup>c</sup> ; <i>S. Enteritidis</i> PT4 <sup>e</sup> ; <i>S. Typhimurium</i> <sup>f</sup> ; <i>S. Typhimurium</i> DT124 <sup>b</sup> ; <i>S. Typhimurium</i> 4, 5, 12:i-(R-type ASSuT) <sup>d</sup> ; <i>S. Enteritidis</i> and <i>S. Typhimurium</i> other others <sup>i</sup> ; <i>S. Enteritidis</i> (B, C1, C2, D, E) and <i>S. Choleraesuis</i> <sup>j</sup> ; <i>S. Typhimurium</i> , <i>S. Blockey</i> , <i>S. Newport</i> , <i>S. Heidelberg</i> and <i>S. Enteritidis</i> <sup>k</sup> ; <i>Salmonella</i> B, C1, C2, D1, E2, F, G2 <sup>l</sup> ; <i>Salmonella</i> B, C1, C2, D1, E1, E2 <sup>g</sup>	Elementary and junior high schools: median $\pm$ SD: 80.9 $\pm$ 35.9 hours; Nursery schools: median $\pm$ SD: 64.8 $\pm$ 21.6 hours <sup>a</sup> ; <24 hr->7 d (median: 1-3 d) <sup>b</sup> ; 3-16 d (median: 8 d) <sup>c</sup> ; 1 - 127 hours (median: 40 hours; IQR: 27-56 hours) <sup>d</sup>		$\geq 4$ ->22 weeks from exposure <sup>e</sup> 1-18 weeks (median: 4.5 weeks; max 7 for almost all) <sup>f</sup> Age <3 months: mean 12.1 d from first positive sample; Age 3 months-1 year: 81.3 d <sup>g</sup> 100%, 50%, 14%, 7%, 3% positive at week 0, 3, 7, 10, 14 after infection <sup>h</sup> ; Mean ( $\pm$ SD) d of shedding from admission to hospital - <i>S. Typhimurium</i> : 5.4 weeks ( $\pm$ 6.2) - <i>S. Enteritidis</i> : 3.8 weeks ( $\pm$ 3.7) - Other <i>Salmonella</i> : 5.4 weeks ( $\pm$ 13.6) <sup>i</sup> ; Mean ( $\pm$ SEM) duration of shedding from first positive stool culture after admission to the hospital <2 yrs (n=23): 19.9 d ( $\pm$ 5.8) $\geq 2$ yrs (n=22): 12.3 d ( $\pm$ 1.9) <sup>j</sup> 7/12, 4/11, 0/9 and 0/12 isolates positive 7 d after start of study, 1, 8 and 26 weeks after end of study, respectively <sup>k</sup> Up to first of at least 2 negative cultures: 1-111 d (mean $\pm$ SEM: 28.5 d $\pm$ 9.4; median: 12 d); up to last positive culture: 1-77 d (mean $\pm$ SEM: 20.9 d $\pm$ 6.8 d; median: 11 d) <sup>l</sup>		<sup>a</sup> Abe 2004[72] <sup>b</sup> Cowden 1989[75] <sup>c</sup> Matsui 2004[80] <sup>d</sup> Raguenaud 2012[82] <sup>e</sup> Balfour 1999[73] <sup>f</sup> Lennox 1954[79] <sup>g</sup> Sheu 1990[83] <sup>h</sup> Barbara 2000[74] <sup>i</sup> El-Radhi 1992[76] <sup>j</sup> Huang 2012[77] <sup>k</sup> Kazemi 1973[78] <sup>l</sup> Nelson 1980[81]
Typhoid fever	<i>S. Typhi</i> <sup>c</sup> ; <i>S. Typhi</i> PTA <sup>b</sup> ; <i>S. Typhi</i> PT34 <sup>d</sup>	5-34 d (median: 14-15 d) <sup>a</sup> ; Mean: 19.5 d; median: 19 d <sup>b</sup> ; 4-20 d (median 18 $\pm$ 5 d) <sup>c</sup>		All stool samples negative 4 months after being clinically cured <sup>d</sup>		<sup>a</sup> Galloway 1966[85] <sup>b</sup> Taylor 1974[86] <sup>c</sup> Anita 2012[84] <sup>d</sup> Usera 1993[87]
Paratyphoid fever						-
Shigellosis	<i>S. sonnei</i> <sup>a, b, e</sup> ; <i>S. sonnei</i> and <i>S. flexneri</i> <sup>d</sup> ; <i>S. sonnei</i> , <i>S. flexneri</i> (1b, 2a, 2b, 3, 3a, 3b, 4a) and <i>S. dysenteriae</i> <sup>c</sup>	median: 2 d <sup>a</sup> ; 1-6 d (mean: 2.3 d) <sup>b</sup>		1-10 d from start of therapy (mean: 5.0 d) <sup>c</sup> ; Time to negative culture >48 hours after start of the study: 33/47 (70%); Culture positive after 5 d: 22/42 (52%), after 10 d: 20/41 (49%) <sup>d</sup>	Daycare centre 1: allowed to return on appropriate antimicrobial therapy after diarrhea had ceased, and were isolated in separate room until 2 negative successive stool cultures. Daycare centre 2: closed until family running the centre had 2 negative successive negative stool culture after antimicrobial therapy. Transmission ceased within 2 d after interventions. <sup>e</sup>	<sup>a</sup> Keene 1994[68] <sup>b</sup> Makintubee 1987[89] <sup>c</sup> Haltalin 1967[88] <sup>d</sup> Haltalin 1972[66] <sup>e</sup> Tauxe 1986[90]

Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
<b>Parasitic infections</b>						
Giardiasis	<i>G. lamblia</i> <sup>a</sup>				Group 1: Readmission to daycare centre after completion of treatment, and two <i>Giardia</i> -negative stool examinations by the health department. Group 2: Readmission when asymptomatic, with continued treatment and follow-up testing in the centre. Group 3: Readmission when asymptomatic, with continued treatment and follow-up testing in the centre. At the end of the 6-month follow-up period, no control strategy was associated with significantly lower prevalences of <i>Giardia</i> , although the 6-month prevalence in all 3 groups were significantly lower than the prevalences at the time of intervention. <sup>a</sup>	<sup>a</sup> Bartlett 1991[91]
<b>Airborne diseases</b>						
Seasonal influenza	Influenza A <sup>d,e</sup> ; Influenza A H3N2 <sup>a</sup> ; Influenza A H3N2/Port Chalmers/73 <sup>b</sup> ; Influenza A/Hong Kong variant <sup>g</sup> ; Influenza B <sup>a,d,f</sup>			Influenza A Mean ± SD: 6.8±1.7 (culture), 7.3±2.5 d (antigen) from illness onset <sup>a</sup> ; <7-21 d from occurrence of fever or hospital admission <sup>b</sup> ; 74%, 70%, 10%, 5%, 0%, 0%, 0% of samples were positive 0-3, 4-7, 8-11, 12-15, 16-19, 20-23 and 24-28 d after onset of symptoms, respectively. <sup>d</sup> ; 100%, 98%, 60%, 48% of samples were positive on d 1, 2, 3, 4 of hospitalisation, respectively <sup>e</sup> Influenza B Mean ± SD: 6.2±1.3 d (culture), 4.6±1.0 d (antigen) from illness onset <sup>a</sup> ; 79%, 68%, 42%, 22%, 0%, 0%, 0% of samples were positive 0-3, 4-7, 8-11, 12-15, 16-19, 20-23 and 24-28 d after onset of symptoms, respectively <sup>d</sup> ; 98%, 95%, 93%, 73%, 43%, 14% of samples were positive on d 1, 2, 3, 4, 5, 6 of illness, respectively <sup>f</sup> Time span during which shedding took place: Influenza A virus was shed from 5-8 d before onset of symptoms to 12-15 d after onset of symptoms. <sup>d</sup> Influenza A was shed to at least 9 days from day of admission <sup>g</sup> Influenza B virus was shed from 0-3 d before onset of symptoms to 12-15 d after onset of symptoms. <sup>d</sup>	School closure can reduce transmission of seasonal influenza among school-children. <sup>c</sup> Standard class closure (2 d-class closure, carried out the day following student absentee rates due to influenza or influenza-like illness reaching 10%) is effective for mitigating outbreaks in elementary schools. Non-standard class closure (different approaches (e.g. 1 d class closure carried out after 10% absentee rate, or class closures carried out ≥2 d after a 10% student absentee rate) relatively ineffective at mitigating an influenza outbreak with a class, but subgroup analyses revealed that "1 d class closure" effectively interrupted outbreaks within 1 week and resulted in outbreaks of shorter duration than those controlled by "standard class closures". <sup>h</sup>	<sup>a</sup> Sato 2005[98] <sup>b</sup> Hall 1975[94] <sup>c</sup> Jackson 2013[97] <sup>d</sup> Frank 1981[93] <sup>e</sup> Hall 1978[95] <sup>f</sup> Hall 1979[96] <sup>g</sup> Brocklebank 1972[92] <sup>h</sup> Sugisaki 2013[99]
Scarlet fever	Group A <i>streptococci</i> type emm3 <sup>a</sup>				Minimum exclusion of cases from school was 24 hours (though in practice usually 48 hours; with penicillin treatment), but not effective <sup>a</sup> ; Excluded from nursery for 5 d after the start of treatment with penicillin. Closure (once on advice, once for holidays). Symptoms of the last reported case began on 1 d after school closure. <sup>b</sup>	<sup>a</sup> Lamden 2010[100] <sup>b</sup> Hoek 2006[101]

Disease/agent	Specification	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Refs
Streptococcal pharyngitis	Group A streptococci <sup>a</sup>				Children with positive throat cultures for group A streptococcal pharyngitis should complete a full 24 hours of antibiotic therapy before returning to school <sup>a</sup>	<sup>a</sup> Snellman 1993[102]
Streptococcal impetigo	-	-		-	-	
Respiratory Syncytial Virus (RSV), fever and respiratory tract infections	RSV			1–21 d from hospitalisation (mean: 6.7 d) <sup>a</sup> ; For all children in the study who did or did not attend the clinic: 1–14 d from symptom onset or first sample (mean: 4.5 d (95% CI 4.0–5.3); median: 4 d (IQR 2–6 d)). For children who attended clinic only: mean: 7.69 d from symptom onset (95%CI 6.41–8.98). <sup>b</sup> ; Median: 11.5 d from hospital admission (IQR 6.5–18.5) <sup>c</sup> ; 74%, 72%, 11%, 0%, 8%, 7%, 4% of samples were positive on d 0–3, 4–7, 8–11, 12–15, 16–19, 20–23 and 24–27, respectively, from onset of symptoms <sup>e</sup> ; 3–11 d after 1st positive sample (mean: 4–6 d) <sup>f</sup> ; Probability of virus shedding by d after onset of illness: 100%, 98%, 90%, 80%, 63%, 53%, 45%, 33%, 18%, 13%, 5%, 2% on d 0–2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13–16, respectively <sup>g</sup> ; 6–36 d; mean 3.9 d (<16 y), mean 9 d (<2 y) <sup>h</sup> ; Time span during which shedding took place: RSV was isolated during a period from 2 d before to 9 d after onset of illness <sup>d</sup> ; RSV was found 1–4 d before onset of symptoms up to 24–27 d after onset of symptoms <sup>e</sup>		<sup>a</sup> Hall 1976[103] <sup>b</sup> Okiro 2010[106] <sup>c</sup> von Linstow 2006[109] <sup>d</sup> Sterner 1966[107] <sup>e</sup> Frank 1981 <sup>f</sup> Hall 1978 [105] <sup>g</sup> Sung 1993 <sup>h</sup> Hall 1976 [104]
Infectious mononucleosis	Epstein-Barr virus <sup>a</sup>			75/101 (74.3%), 21/38 (55.3%), 19/38 (50.0%), 13/21 (61.9%) of samples were positive 0–3, 4–8, 9–28 and ≥29 weeks after onset. <sup>a</sup>		<sup>a</sup> Sumaya 1985[110]
<b>Other transmissible diseases of common among children</b>						
Roseola infantum (exanthema subitum)	HHV-6 <sup>b</sup>	Serial interval 5–15 d (average, 10 d) <sup>a</sup>		Up to 60–90 d (intermittent) <sup>b</sup>		<sup>a</sup> Barenberg 1939[111] <sup>b</sup> Suga 1998[112]
Fifth disease (erythema infectiosum, parvovirus infection)	-	-	-	-	-	-
Impetigo Staphylococcal	-	-	-	-	-	-
Hospital colonisation by resistant microorganisms	-	-	-	-	-	-
MRSA infection						-

d: days; SD: standard deviation; yr(s): year(s)

## Results other data sources

Three major data sources underlie this chapter: 1) Websites from key health organisations, 2) Handbooks and 3) a literature review from 2001 on the same subject as the current review.

An overview of the findings from these sources can be found in Table 5.3. For each disease, data are presented from

- WHO website (<http://www.who.int/en/>)
- CDC website (<http://www.cdc.gov/>)
- The American Academy of Pediatrics (AAP) 2012 'Red Book' [113] and The 2009 'Managing diseases in childcare and schools. A quick reference guide' [114].
- Richardson et al., 2001 [115]

In Table 5.1, we first summarise the characteristics of the 2001 literature review by Richardson et al. [115]. The authors report the lack of knowledge about the incubation period and period of infectiousness of certain communicable diseases as one of their major findings. The authors state that for ease of presentation only the highest quality references are provided in their review. Nonetheless, they report much of the data to be derived from lower level of evidence, i.e. 'case reports with <5 subjects, or poorly substantiated larger studies', or 'opinion or clinical experience of experts (not supported by published data)', see Table 5.2A.

**Table 5.1. Characteristics of Richardson et al. 2001**

<b>Author</b>	Richardson
<b>Year, journal</b>	2001, <i>Pediatr Infect Dis J</i>
<b>Background</b>	In practice, information about incubation periods and periods of infectiousness is usually obtained from textbooks and manuals. This information and recommendations for exclusion periods are also available in various national and local guidelines for the control of communicable diseases in schools and preschools. The values in these sources are rarely referenced, and the origin of the data is unclear.
<b>Aim</b>	To thoroughly review the incubation period and period of infectiousness of childhood infections and to determine whether exclusion would influence secondary transmission (commissioned by the UK Government Department for Education and Employment and the Department of health, in order to prepare national guidelines on the control of communicable diseases in schools and preschools)
<b>Infective agent(s)</b>	41 Infections, selected on the basis that they are common, or are a particular concern, in immunocompetent children of school or preschool age
<b>Outcome</b>	Incubation period, period of infectiousness, effectiveness of exclusion. In absence of information on period of infectiousness, and if the incubation period was known, serial interval was used to estimate the period of infectiousness
<b>Period</b>	1966–1998
<b>Search date</b>	NR
<b>Search terms</b>	NR
<b>Sources</b>	MEDLINE, hand search and United Kingdom authorities on individual infections
<b>Inclusion criteria</b>	If more than 1 paper yielded the required information, then the most useful papers were identified based on the number of cases reported, the age of the cases (school age preferred), the location (school preferred to community or family setting) and geography (industrialized world preferred).
<b>Included</b>	>3000 references were obtained and read, ~20% yielded useful information.
<b>Results</b>	Exclusion periods were established in consensus with members of professional groups represented by the authors. Reasons for not recommending an exclusion period were: - not fully effective because infectious before onset of disease - not fully effective because asymptomatic cases occur and may be involved in transmission - not required as illness is mild in childhood
<b>Limitations</b>	Very limited information available on study characteristics and populations

**Table 5.2. A. Levels of evidence used in the studies included in the review by Richardson et al. 2001**

Level of evidence	Source of data
I	Systematic review, metaanalysis or well-designed epidemiologic or experimental study with $\geq 50$ subjects
II	Well-designed epidemiologic or experimental study with 5 - 50 subjects
III	Case reports with < 5 subjects, or poorly substantiated larger study
IV	Opinion or clinical experience of experts (not supported by published data)

**Table 5.2. B. Level of grades of recommendation used in the studies**

Grade of recommendation	Definition
A	Derived from Level 1 evidence of period of infectiousness and/or effectiveness of exclusion
B	Derived from Level 2 evidence of period of infectiousness and/or effectiveness of exclusion or Level 1–2 evidence of duration of shedding and/or serial interval
C	Derived from Level 3 or 4 evidence of period of infectiousness, effectiveness of exclusion, duration of shedding and/or serial interval

The authors attach the following levels of evidence to their recommendations (restricted here to the diseases in this review):

- Level A evidence: varicella
- Level B evidence: measles, mumps, rubella, pertussis, meningococcal disease, EHEC, hepatitis A, influenza, scarlet fever, streptococcal infection (any, incl pharyngitis), infectious mononucleosis, roseola infantum, erythema infectiosum, hospital colonisation by resistant microorganisms, MRSA infection
- Level C evidence: enterovirus infections, gastroenteritis by adenovirus, by astrovirus, by caliciviruses, by rotavirus; campylobacteriosis, EPEC/EIEC/ETEC, shigellosis, salmonellosis, typhoid fever, paratyphoid fever, giardiasis.

Google search was used to identify guidelines and recommendations for underlying references or relevant recommendations that were not identified in the peer-reviewed search.

Some recent examples of reports or tables by national institutes include:

- 'Guidance on infection control in schools and other childcare settings' by Public Health England, 2014 [116].
- 'Communicable disease guidelines: For teachers, childcare workers, local government authorities and medical practitioners' by Government of Western Australia, 2013 [117]
- 'Management of infectious disease in childcare facilities and other childcare settings' by Ireland Health Protection Surveillance Centre, 2012 [118].
- 'National Board of Health Guideline: Infectious diseases in children and adolescents (in Danish)' by Danish National Board of Health, 2012 [119].
- 'Exclusion Criteria for Childcare and Childminding Settings: Recommended time to be kept away from day-care and childminding' (poster) by Health Protection Scotland, Health Protection Network, et al., 2011 [120].

However, original information sources are generally not provided. As the scope of this project was not to compare the different recommendations in the different countries, but to identify the scientific information behind them, they were not further described in this report.

**Table 5.3. Overview of relevant outcomes from all other data sources: World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), Red Book (RB), Quick Reference guide (RG), Richardson 2001 (R2001)**

Disease/agent	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Reference
<b>Vaccine preventable diseases</b>					
Measles	<b>WHO:</b> 7–18 (often, 10–12) days from exposure to the onset of fever [121]; <b>RB:</b> Generally 8–12 days from exposure to onset of symptoms; <b>CDC:</b> 7–21 (14) days to a rash [122–124]; 10–12 days to prodrome [123, 125] <b>R2001:</b> 6–19 (13) days	<b>WHO:</b> 4 days before the rash until 1–2 days after a rash [121]; <b>RB:</b> 4 days before the rash to 4 days after a rash; <b>CDC:</b> 4 days before to 4 days after a rash onset [123–125] <b>R2001:</b> ND (but at least 1–2 days before a rash)	<b>WHO:</b> Following a rash onset, measles excretes for very short period (about 5 days) [126]; <b>CDC:</b> Beginning with the prodrome until 3–4 days after a rash onset; <b>R2001:</b> -2 to +3 days	<b>RB:</b> Until 24 hours after treatment has been initiated; <b>RG:</b> At least 2 weeks after a rash in the last case for unimmunised people who have been exempted from measles immunisation within 72 hr of exposure; <b>CDC:</b> 4 days after a rash for cases; 21 days after a rash in the last case for persons who have been exempted from measles vaccination within the appropriate time; <b>R2001:</b> 5 days from onset of a rash	[121–126]
Meningococcal disease	<b>WHO:</b> 2–10 (average, 4) days [127], 1–10 days, usually <4 days [128], Symptoms of invasive meningococcal disease (IMD) usually occur 1–4 days after infection [129]. <b>RB:</b> 1–10 days, usually <4 days; <b>RG:</b> For meningococcus and S pneumonia: <4 days; for Hib: unknown, <b>CDC:</b> 2–10 (usually, 3–4) days [123], 1–14 days [124]	<b>RB:</b> Up to 24 hours after initiation of effective antimicrobial treatment; <b>CDC:</b> Communicability is generally limited [123]	<b>RG:</b> For <i>N. meningitidis</i> , <i>S. pneumoniae</i> and <i>H. influenzae</i> , meningitis: shedding in faeces can continue: until after 24 hr of antibiotics; <b>R2001:</b> Untreated: median, 9 months; Treated: 1–2 days from start of chemoprophylaxis	<b>RG:</b> Should be excluded as soon as it is suspected; <b>CDC:</b> Closing schools or universities is not recommended for outbreak control [130] <b>R2001:</b> 48 h from start of treatment	[123, 124, 127–130]
Mumps	<b>WHO:</b> 14–28 (averages, 16–18) days [131]; <b>RB:</b> 12–25 (usually, 16–18) days; <b>CDC:</b> 12–25 (usually, 16–18) days [123, 124, 130, 132]; <b>R2001:</b> 15–24 (mean, 19) days	<b>WHO:</b> 2 days before up to 9 days after swelling of the parotid glands [131]; <b>RG:</b> 1–2 days before to 5 days after swelling of glands, although virus can be isolated from saliva from 7 days before to 9 days after swelling of glands; <b>CDC:</b> 7 days before to 11–14 days after parotitis onset [130]; 3 days before to 4 after onset of active disease [123, 133, 134]	<b>RB:</b> Virus has been isolated from saliva from 7 days before through 8 days after onset of swelling; <b>CDC:</b> Virus has been isolated from saliva 7 days before to 9 days after onset of parotitis [123] <b>R2001:</b> -7 to +4 days	<b>RB:</b> Until 5 days after onset of parotid gland swelling; <b>RG:</b> Until 5 days after onset of parotid gland swelling; Exclude exposed children who have not been immunised until they become immunised or, if they are not immunised because of an accepted exemption, continue to exclude them until the health department determines it is safe. This may be as long as a month after the last case; <b>CDC:</b> 5 days after onset of parotitis [135]; Students who have been exempted from mumps vaccination should be excluded until the 26th day after the onset of parotitis in the last person [130]; <b>R2001:</b> 5 days from onset of parotitis	[123, 124, 130–135]
Pertussis	<b>WHO:</b> 6–20 (usually 9–10) days [136]; <b>RB:</b> 5–21 (usually 7–10) days; <b>CDC:</b> 4–21 (usually 7–10) days [123, 124, 137–141]; <b>R2001:</b> 5–21 days, usually 7 d, rarely >10 days	<b>WHO:</b> 3 weeks or more following coughing for untreated patients, although communicability diminishes rapidly after the catarrhal stage. Chronic carriers of B. Pertussis are uncommon [136]; <b>RB:</b> Most contagious during the catarrhal stage and the first 2 weeks after cough onset; <b>CDC:</b> Most infectious during the catarrhal period and the first 2 weeks after cough onset (i.e., approximately 21 days) [123, 142]	<b>R2001:</b> Untreated: 60% > 2 weeks, 20% > 6 weeks; Treated: <7 days	<b>RB:</b> Until 5 days of appropriate antimicrobial therapy course completed; <b>CDC:</b> Until 5 days of a full course of antimicrobial treatment; Untreated: 21 days from onset of cough [142]; <b>R2001:</b> Treated: 5 days from starting antibiotics; Untreated: at least 3 weeks	[123, 124, 136–142]
Rubella	<b>WHO:</b> 12–23 (average, 18) days [143]; <b>RB:</b> 14–21 (usually, 16–18) days; <b>CDC:</b> 12–23 (14–17) days [Ref. 123, 124, 130, 144]; <b>R2001:</b> 15–20 (17) days	<b>RB:</b> Although virus can be found in nasopharyngeal secretions from 7 days before to 14 days after onset of a rash, the period of maximal communicability extends from a few days before to 7 days after onset of a rash; <b>CDC:</b> most infectious when a rash is erupting, but they can shed virus 7 days before to 7 days after a rash onset [130]	<b>WHO:</b> Virus can be found in nasopharyngeal samples from 1 week before the onset of the rash to 2 weeks after, with maximal shedding occurring 1–5 days after a rash onset [143]; <b>CDC:</b> 7 days before–5–7 days after a rash onset [123, 144]; <b>R2001:</b> -13 to +6 (usually -7 to +2) days, and most before a rash	<b>RB:</b> Until 6 days after onset of a rash <b>RG:</b> Until 6 days after the rash; For outbreaks, exclude exposed children who have not been immunised (or, if older than 4–6 years, received <2 doses of vaccine) until they become immunised or, if they are not immunised because of an accepted exemption, continue to exclude them until the health department determines it is safe. This may be more than 3 weeks; <b>CDC:</b> Outbreak setting: 23 days after the onset of a rash of the last reported case [130]; Cases: infectious period (i.e., 5–7 days after a rash onset) [144]; <b>R2001:</b> 5 days from onset of a rash	[123, 130, 143, 144]



Disease/agent	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Reference
Varicella	<b>WHO:</b> 10–21 (usually, 14–16) days from exposure to a rash [145]; <b>RB:</b> 14–16 days, occasionally is as short as 10 days or as long as 21 days after exposure to a rash; <b>CDC:</b> 10–21 (usually, 14–16) days [146, 147] [123, 124]; <b>R2001:</b> 11–20 (median, 15) days	<b>WHO:</b> Until all lesions have crusted over [145]; <b>RG:</b> May be contagious a day before the rash, most contagious while the rash is spreading until all the blisters have scabs and no new blisters are forming; <b>CDC:</b> 1–2 days before to 4–7 days after a rash onset [123, 146, 147]; <b>R2001:</b> -4 to +5 days, usually -1 to +2 days		<b>RB:</b> Until all lesions have dried and crusted (usually 6 days after onset of a rash); <b>CDC:</b> Until lesions have crusted over [146] <b>R2001:</b> 5 days from start of skin eruption	[123, 124, 145–147]
<b>Food and waterborne diseases</b>					
<b>Viral gastrointestinal infections</b>					
Enterovirus infections (non-polio, non-hand-foot and mouth)	<b>R2001:</b> 2–7 days <b>RG:</b> For the most common cause of viral meningitis due to enterovirus: 3–6 days		<b>CDC:</b> Can be shed in stool for weeks after infection, from the respiratory tract for 1 to 3 weeks or less [148]. <b>RG:</b> For enterovirus viral meningitis shedding of the virus in feces can continue for several weeks, but shedding from respiratory tract usually lasts a week or less. <b>R2001:</b> 1–3 weeks		[148]
Gastroenteritis by adenovirus	<b>WHO:</b> 3–5 days [149]; <b>RB:</b> 3–10 days; <b>R2001:</b> 8–10 days	<b>RB:</b> Most communicable during the first few days of an acute illness	<b>RB:</b> Persistent and intermittent shedding for long periods, even months; <b>R2001:</b> >7 but < 14 days	<b>R2001:</b> 24 h from last episode of diarrhea	[149]
Gastroenteritis by astrovirus	<b>WHO:</b> 3–5 days [149]; <b>RB:</b> 1–4 days <b>R2001:</b> 3 days		<b>RB:</b> Median, 5 days after onset of symptoms; <b>R2001:</b> 2–30 days	<b>R2001:</b> 24 h from last episode of diarrhea	[149]
Gastroenteritis by norovirus/calicivirus	<b>WHO:</b> 12–48 (median, 36) hours [149]; <b>RB:</b> 12–48 hours; <b>CDC:</b> 12–48 hours [35, 124, 150]; <b>R2001:</b> calicivirus, 1–3 days Norovirus, 4–77 (median, 36) hours		<b>WHO:</b> Virus shedding, as detected by electron microscopy, stops soon after onset of symptoms, but is detectable by RT-PCR for up to 5 days [151]; <b>RB:</b> 4 days after exposure and may persist for as long as 3 weeks; <b>CDC:</b> Average: 4 weeks following infection, Peak: 2–5 days after infection [152]; <b>R2001:</b> 0–7 hours	<b>RG:</b> Exclude under conditions^; <b>CDC:</b> Acute phase of illness, and a period following recovery while the person is still shedding virus at high levels (usually 24–72 hours); <b>R2001:</b> 24 h from last episode of diarrhea	[35, 124, 149–152]
Gastroenteritis by rotavirus	<b>WHO:</b> 3–5 days [149], about 48 hours [121], children: 1–3 days; <b>RB:</b> 1–3 days [153]; <b>CDC:</b> <48 hours [123]; <b>R2001:</b> 2–4 days		<b>WHO:</b> Several days in very high concentrations in the stools and vomitus [153]; <b>RG:</b> Virus is present before diarrhea begins and can persist for up to 3 weeks after the illness; <b>CDC:</b> 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms [123]; <b>R2001:</b> 1–8 days (mx 3–5 days)	<b>RG:</b> Exclude under conditions^; <b>R2001:</b> 24 h from last episode of diarrhea	[39, 121, 123, 149, 153]
<b>Other viral infections</b>					
Hepatitis A	<b>WHO:</b> 15–45 (mean, 30) days [154, 155], 2–6 weeks (usually, 25–28 days) [149], 15–50 days [151]; <b>RG:</b> 15–50 (average, 30) days; <b>CDC:</b> 15–50 (usually, 28) days [123, 124, 130]; <b>R2001:</b> 25–50 (median, 33) days; as short as 15 days	<b>RG:</b> Most infectious in the 2 weeks before onset of symptoms; the risk for transmission is minimal 1 week after onset of jaundice. <b>CDC:</b> 2 weeks before to 1 week after onset [123, 124]; <b>R2001:</b> -2 weeks to some point 0–+8 days	<b>WHO:</b> Begins late in the incubation period, peaks just before onset of symptoms (usually dark urine), and falls to barely detectable levels as the clinical illness evolves. The virus is present in blood for 7–14 days, with a peak before the onset of symptoms [154, 155]; <b>CDC:</b> 1–2 weeks before to 1–3 weeks after onset of illness [123, 156] <b>R2001:</b> +12 days, median, +1 days, Usually -10 to +3 days; mx -3 to -2 days	<b>RB:</b> Until 1 week after onset of jaundice; <b>R2001:</b> <5 y: 5 days, ≥5 y: none	[123, 124, 130, 149, 151, 154–156]



Disease/agent	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Reference
<b>Bacterial infection<sup>^</sup></b>					
Campylobacteriosis	<b>WHO:</b> 1–11 (usually, 2–5) days [149, 157, 158]; <b>RB:</b> 2–5 days but can be longer; <b>CDC:</b> 2–4 days [124]; <b>R2001:</b> 1–3 days		<b>WHO:</b> Can continue for 2–3 weeks [149]; <b>RB:</b> 2–3 weeks; <b>R2001:</b> 1–11 (median, 4) days	<b>RG:</b> Exclude under conditions <sup>^</sup> ; <b>R2001:</b> 24 h from last episode of diarrhoea	[124, 149, 157, 158]
Escherichia coli	<b>WHO:</b> 1–10 (median, 3–4) days [149, 159, 160], 1–5 days [157]; <b>RG:</b> 10 hours to 6 days; E coli O157:H7 averages 3 to 5 days, but ranges from 1 to 8 days; <b>CDC:</b> Non-STEC: 9 hours–3 days, STEC: 3–4 (range 1–10) days [124] <b>R2001:</b> EHEC: 1–10 (median, 4) days, EPEC: 2–48 (median, 18) hours, EIEC: 1 hour–6 days (mean, 3 days), ETEC: 3 hours–7 days (median, 4 days)	<b>RG:</b> Until diarrhoea resolves and test results from 2 consecutive stool cultures are negative for the E coli O157:H7 bacteria that caused the problem.	<b>WHO:</b> 7–13 days(160); Children: average 13 to 17 days [159]; <b>R2001:</b> EHEC: 2–62 (median,17) days, EPEC: <12 days, ETEC: <5 days	<b>RB:</b> Until diarrhoea resolves and results of 2 stool cultures are negative; <b>R2001:</b> EHEC (O157): 2 negative stools, Others: 24 h from last episode of diarrhoea	[124, 149, 157, 159, 160]
Salmonellosis (non-typhoid)	<b>WHO:</b> 6–48 hours, occasionally up to 4 days(149); 8–72 hours [157] <b>RB:</b> 6–72 (usually, 12–36) hours; <b>CDC:</b> 6–72 hours, but illness usually occurs 12–36 hours after exposure [124] <b>R2001:</b> 4–5 days, median, 16 hours		<b>WHO:</b> For several weeks or, in some cases, months [149]; <b>RB:</b> 12 weeks after infection, about 45% of children < 5 years excrete organisms, compared with 5% of older children and adults; <b>R2001:</b> < 5 y: <12months (median, 10 weeks), ≥ 5 y: <12 (median, 4) weeks.	<b>RB:</b> Until diarrhoea resolves; <b>R2001:</b> < 5 y: at least one negative stool ≥ 5 y: 24 h from last episode of diarrhoea	[124, 149, 157]
Typhoid fever	<b>WHO:</b> 1–14 (usually, 3–5) days [161–163]; 3 days up to 1 month (usually 8–14 days) [121]; 10–20 days (range 3 days–8 weeks) [149]; <b>CDC:</b> 6–30 days [124]; <b>R2001:</b> 5–34 (median, 15–21) days (3 d – 3 m quoted)	<b>WHO:</b> From the symptomatic period for 2 weeks. 2–5% of infected cases remain carriers for several months [121]; <b>R2001:</b> ? >2 w. Carriers indefinite	<b>WHO:</b> Excretion may occur after recovery or by asymptomatic carriers and may be lifelong unless treated [149]; <b>R2001:</b> Throughout incubation period, after onset 60% children >2 weeks and 15% >4 weeks	<b>R2001:</b> < 5 y: at least one negative stool ≥ 5 y: 24 h from last episode of diarrhoea	[121, 124, 149, 161–163]
Paratyphoid fever	<b>WHO:</b> 10–20 days (range 3 days–8 weeks) [149]; <b>CDC:</b> 6–30 days [124]; <b>R2001:</b> 2–3 weeks		<b>WHO:</b> Excretion may occur after recovery or by asymptomatic carriers and may be lifelong unless treated [149]; <b>R2001:</b> ~6% become persistent excreter	<b>R2001:</b> < 5 y: at least one negative stool ≥ 5 y: 24 h from last episode of diarrhoea	[124, 149]
Shigellosis	<b>WHO:</b> 1–3 days (average, 24 hours)[89, 149, 158, 164–167]; <b>RB:</b> 1–7 (usually,1–3) days; <b>CDC:</b> 12–96 hours(124); <b>R2001:</b> 1–6 (median, 2) days	<b>WHO:</b> The infection usually lasts for 4–7 days and is self-limiting [89, 165]	<b>WHO:</b> 30 days [89, 165]; <b>RG:</b> Untreated, Shigella persists in stool for up to 4 weeks; <b>R2001:</b> Untreated: 1–78 days, mean 27 days, Treated: 1–14 days, mean 7 days	<b>RB:</b> Until diarrhoea resolves and results of 2 stool cultures are negative; <b>RG:</b> Exclude under conditions <sup>^</sup> ; <b>R2001:</b> < 5 y: at least one negative stool ≥ 5 y: 24 h from last episode of diarrhoea	[89, 124, 149, 158, 164–167]
<b>Parasitic infections</b>					
Giardiasis	<b>WHO:</b> 7–12 days [168, 169], 4–25 (usually, 7–10) days(149), 1–4 weeks, (mean, 10) days [157]; <b>RB:</b> 1–3 weeks; <b>CDC:</b> 1–2weeks [124]; <b>R2001:</b> 5–20 (median, 7) days	<b>RB:</b> As long as the infected person excretes cysts;	<b>WHO:</b> 6 months [168, 169]; <b>RB:</b> Variable, can range from weeks to months; <b>R2001:</b> 1–5 weeks, mean 2 weeks	<b>RG:</b> Exclude under conditions <sup>^</sup> ; <b>R2001:</b> 24 h from last episode of diarrhoea	[124, 149, 157, 168, 169]
<b>Airborne diseases</b>					
Seasonal influenza	<b>WHO:</b> 1–4 (average, 2) days(170); <b>RB:</b> 1–4 (average, 2) days; <b>CDC:</b> 1–4 (average, 2) days [123, 124, 130]; <b>R2001:</b> 1–3 (median, 1.5) days	<b>WHO:</b> Shortly before onset of symptoms and last into the second week [170]; <b>RG:</b> From the day before symptoms appear until at least 7 days after the onset of flu, although virus shedding can be longer; <b>CDC:</b> Adults can transmit 1 day before and 5–7 days after symptoms [124], Children can transmit for over 10 days [123]	<b>WHO:</b> Young children: up to 21 days [171]; <b>CDC:</b> 5–10 days [123], Children: >10 days after symptom onset [124], Peak usually occurs from 1 day before onset of symptoms to 3 days after [130]; <b>R2001:</b> 7–12 days, mean 9 days	<b>RG:</b> No need to exclude, unless the child is unable to participate, meets other exclusion criteria such as fever with behaviour change	[123, 124, 130, 170, 171]

Disease/agent	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Reference
Scarlet fever	<b>RG:</b> 2–8 days, 4–6 days is most common; <b>R2001:</b> 2–4 days		<b>RG:</b> 3–8 days (3–4 weeks in young infants, usually beginning 1 day before symptoms); <b>R2001:</b> Untreated: >2 months, Treated: 3–4 days	<b>RG:</b> No need for exclusion, unless child exhibits rapid or laboured breathing or cyanotic (blue) episodes; the child is unable to participate; the child meets other exclusion criteria such as fever with behavioural change; <b>R2001:</b> 5 days from start of antibiotic treatment	
Streptococcal pharyngitis	<b>WHO:</b> Preceding a rheumatic fever attack is usually 2–3 weeks, but can vary from 5–45 days. In acute glomerulonephritis, may vary from 1–4 weeks [172]; <b>RB:</b> Group A: for pharyngitis usually 2–5 days. For STSS, not known, but as short as 14h in cases associated with subcutaneous inoculation. Group B: in early-onset diseases, it is <7days; in late-onset diseases, not known; <b>R2001:</b> 12 hours–5 days	<b>RG:</b> The risk of transmission from someone who is not sick but carrying the bacteria is minimal;	<b>WHO:</b> Within 24–48h, the organisms reach their maximum number [Ref. 173]; <b>R2001:</b> Untreated: 1–12 (median, 3) months, Treated: <4 days	<b>RB:</b> Until 24 hours after treatment has been initiated and the child is able to participate in activities;	[172, 173]
Impetigo, streptococcal	<b>RB:</b> a 7- to 10 days period between acquisition of group A streptococci on healthy skin and development of lesions have been demonstrated <b>RG:</b> Skin sores develop in 7 to 10 days after bacteria attach to the skin <b>R2001:</b> 2–33 days (median 8 days) [174]		<b>R2001:</b> Several weeks (untreated)	<b>RB:</b> Exclusion until 24 hours after treatment has been initiated <b>RG:</b> Temporarily exclude until exclusion criteria are resolved. Wash the affected area and cover the sores and then exclude the child at the end of the day until child is treated. Readmit to group setting when topical, oral or other systemic antibiotics are started if the sores can be covered and kept dry. <b>R2001:</b> As long as open lesions persist	[174]
Respiratory Syncytial Virus (RSV), fever and respiratory tract infections	<b>RB:</b> 2–8 days, 4–6 days is most common; <b>CDC:</b> Infants and children: 4–6 days (range 2–8 days)[148]	<b>CDC:</b> Most infants and children will recover in 1 to 2 weeks. However, even after recovery, very young infants and children with weakened immune systems can continue to spread the virus for 1 to 3 weeks [148]	<b>RB:</b> Usually 3–8 days, but may last longer, especially in young infants, may continue for 3–4 weeks; <b>CDC:</b> General: 3–8 days. Some infants and people with weakened immune systems can be as long as 4 weeks [148]		[148]
Infectious mononucleosis	<b>RB:</b> 30–50 days; <b>CDC:</b> 4–6 weeks [148, 175], 4–14 days [176]; <b>R2001:</b> 33–49 days	<b>R2001:</b> ≥2 years	<b>RB:</b> Intermittent excretion in saliva may be lifelong after infection; <b>R2001:</b> <16 months, median >5 months		[148, 175, 176]
<b>Other transmissible diseases of common among children</b>					
Roseola infantum (exanthema subitum)	<b>RB:</b> 9–10 days; <b>R2001:</b> 10–15 days	<b>R2001:</b> Lifelong?	<b>R2001:</b> Lifelong?	<b>RG:</b> No need, unless the child is unable to participate or the child meets other exclusion criteria such as fever with behavioural change.	
Fifth disease (erythema infectiosum, parvovirus infection)	<b>RB:</b> 4–14 days but can be as long as 21 days; <b>CDC:</b> 4–14 (max 20) days [148, 177] <b>R2001:</b> 13–18 days	<b>RG:</b> Until the rash appears	<b>R2001:</b> -6 to -3 days	<b>RG:</b> No need, unless the child has an underlying blood disorder, such as sickle cell disease, or a compromised immune system, unable to participate; the child meets other exclusion criteria such as fever with behavioural change; <b>CDC:</b> The greatest risk of transmitting the virus occurs before symptoms of EI develop; therefore, transmission cannot be prevented by identifying and excluding persons with EI. A policy to routinely exclude members of high-risk groups is not recommended.	[148, 177]
Impetigo, Staphylococcal	<b>RB:</b> Variable. A long delay can occur. For toxin-mediated SSSS, usually 1–10 days, for postoperative TSS, can be as short as 12 h. Menses-related cases can develop at any time during menses.			<b>RB:</b> Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing; <b>RG:</b> Wash the affected area and cover the sores and then exclude the child at the end of the day until child is treated; <b>R2001:</b> As long as open lesions exist	
Hospital colonisation by resistant microorganisms				<b>WHO:</b> Isolate infected or colonized patients [178]	[178]

Disease/agent	Incubation period	Period of infectiousness	Period of shedding	Exclusion period	Reference
MRSA infection	<b>RG:</b> Unknown; <b>CDC:</b> 4-22 days [179]	<b>RG:</b> Children who have actively draining sores are more contagious		<b>WHO:</b> Isolate infected or colonized patients [178]; <b>RG:</b> No need for exclusion, unless the child is unable to participate or other exclusion criteria are met, such as fever with behavioural change; <b>CDC:</b> In most cases, not necessary. Exclusion from school and sports activities should be reserved for those with wound drainage ('pus') that cannot be covered and contained with a clean, dry bandage and for those who cannot maintain good personal hygiene	[178, 179]

*CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; RB: Red Book; RG: Quick reference guide, R2001: Richardson 2001*

*\*The reference indicates where the reported information was found, however this does not necessarily be or refer to an original underlying data source and may as such be unsourced*

*^Conditions: stool is not contained in the diaper, diarrhoea is causing 'accidents', stool frequency exceeds 2 or more stools above normal, blood or mucus in stool, stool is all black or very pale, dry mouth, no tears, or no urine output in 8 h, jaundice, the child is unable to participate or other symptoms such as fever with behaviour change*

## 4. Discussion

This report provides an overview of systematically obtained data on the incubation period, period of infectiousness or duration of shedding, and period of exclusion from childcare settings regarding children presenting with selected (symptomatic) infectious diseases. It may serve as one of the building blocks for the development of guidance on exclusion and other control strategies to aid in the prevention of the spread of infectious diseases in childcare settings. This information may be complemented or replaced by non-scientific elements and values as part of a more practically applicable approach.

From a large search in PubMed and Embase, and an additional hand search, a total of 974 peer-reviewed articles were screened in full text for the requested parameters. Of these, 112 were included (covering 119 diseases/agents), 691 were excluded with reasons and 171 could not be retrieved.

Overall, the review showed

- difficulty in finding publications fitting the eligibility criteria that were considered appropriate for this review, i.e. on children with symptomatic infections with clear stratification in case of treatment or vaccination
- great diversity in study characteristics of both included and excluded studies, such as population age, medication or vaccination, diagnostic tools, the inclusion of asymptomatic infections, study design and methodology, which may cause variation in results
- lack of eligible studies on any of the objectives for meningococcal disease, paratyphoid fever, fifth disease, impetigo (streptococcal and staphylococcal), hospital colonisation by resistant pathogens and MRSA infections
- very little information on period of infectiousness; for objective 2 the information is mainly on shedding;
- very little information on period of exclusion and its effectiveness
- questionable reporting and accuracy of definition of key variables (including criterion for establishing date of onset of disease and date of exposure)
- scarcity of referring to scientific literature (or any literature) in narrative reviews, handbooks and websites.

Below, some points for discussion, gaps in information and areas of uncertainty are further described with regard to the results for incubation period, period of infectiousness or duration of shedding, and exclusion period.

First, the approach of the systematic review and adaptation during the process is briefly commented upon.

### 4.1 Systematic review process

This review consists of a first, basic, systematic literature search (performed in August 2014) and an additional, extended, systematic literature search that was carried out after it became clear that significant gaps in evidence remained (performed in May/June 2015). Search terms were extended over the whole range of the review and not restricted to specific diseases/agents.

An expert panel provided input on the results of the original review during two expert panel meetings held on November 13th/14th 2014 and on February 17th 2015. Below, the adaptations to the first protocol made after the panel meetings are summarised.

Adaptations made after panel meetings

The panel meetings led to the following changes that were applied during the review process:

- Adjustments to initial inclusion/exclusion criteria:
  - Pandemic influenza was considered out of scope. Articles were removed from the first draft report accordingly.
  - Immunocompromised/special needs populations were considered out of scope. Articles were removed from the first draft report accordingly.
  - The in/exclusion criteria for seasonal influenza were adapted by not excluding outbreaks. Articles were added accordingly.
  - Case series, preferably providing information on the right tail, were considered appropriate considering the paucity in information (however, Pallas did maintain a lower limit of >5 subjects). The list of excluded articles of the original review was rescreened.
- For this review, it was decided by ECDC to slightly adapt the categorisation of the original list of diseases by
  - Making subgroups for the food and waterborne-diseases: viral, bacterial and parasitic
  - Combining scarlet fever, pharyngitis and impetigo under one heading of *streptococcal* infections
  - Combining non-typhoid, typhoid and paratyphoid under one heading of *salmonella* infections.
- Despite an extensive hand search next to the Pubmed search, the exploration of a second data source was considered worthwhile; it was decided that Embase would be the most appropriate candidate to be searched next to PubMed and this was done.

- Period of infectiousness was considered the most important parameter in the review; yet this was also the parameter with the most data gaps. The search was expanded with additional search terms for period of infectiousness.
- Due to the relative lack of data on exclusion period (objective 3), it was deemed worthwhile to remove the country limits in this search in an updated version of the review.

For the above mentioned adjustments, the original protocol was adapted before the start of the additional review.

## 4.2 Eligibility of articles for the review

Even after screening a large number of references, a relatively limited number of references appeared to be eligible for the review. Reasons for this may be:

- relatively few peer-reviewed studies on the topic
- difficulty in finding the relevant information in a systematic search, as parameters are not always in title/abstract/key words
- studies too small to stratify on relevant variables (such as age, medication) at the same time

Studies that were included in the review, were not without limitations. Main limitations were poor sampling procedure and/or reporting thereof, poor definition of key variables, poor reporting of study population and small sample size. Limitations were added into the extraction tables. Some papers frequently cited in the literature did not fulfil our eligibility criteria, e.g. the 1964 publication by Hoagland [180] for infectious mononucleosis and the 1997 publication by Moser et al. [181] for influenza (mainly because they describe adults).

Below, we address some of the eligibility issues and causes for variation in results in more detail.

## 4.3 Study characteristics possibly causing variation in results

The nature of the infections may influence the ability to measure its characteristics. Cases may acquire their infection from one source (common source infection) and exposure may occur in less than one incubation period (point source infection), rendering its measurement relatively straightforward; Exposure may also occur over multiple incubation periods (continuous source infection) and infection often spreads from person to person (propagated infection), which may complicate measurement. In addition, several other characteristics may influence results, including the definition of the parameters to be measured, population characteristics, laboratory characteristics and study design characteristics. These are discussed below.

### Definition and measurement of incubation period and period of infectiousness or shedding

#### *Incubation period*

The incubation period represents the time from infection to clinical onset. For determining the incubation period it is important that authors accurately define their symptoms of onset, because some diseases have several symptoms with different timing, which would result in a different duration of incubation period. A complication, especially for diseases with longer periods of incubation, is that accurate registration of both the start of symptoms and of exposure to the infectious agent most often relies on good recall by patients and this may influence the exact incubation period.

Distributions in incubation periods are typically right skewed (log normal) and distributions may reflect various biological variations, e.g. in infectious dose, in replication times of the pathogen, or in levels of susceptibility among host populations. There are indications from the literature for an inverse association between infectious dose/viral load and the incubation period (e.g., Poulsen et al. [19] and Abe et al. [72]). Since these biological factors are usually not presented in the included articles (although study design may give information on infectious dose, see 'Study design and methodology'), it is not clear whether variation in outcomes between studies can be explained by these.

In the first part of the review, in some cases, serial intervals were extracted and used as a proxy for the incubation period when the latter were not available. For highly infectious diseases and in settings with frequent contact between subjects, the serial interval is likely to be a good approximation of the incubation period. However, in general, a limitation of serial intervals is that the moment of exposure of a contact is not usually known and for diseases that are not infectious from the start of symptoms, it might overestimate the length of the incubation period and for those that are infectious before the start of symptoms, it might underestimate the length of the incubation period.

### **Period of infectiousness**

The period of infectiousness represents the time interval during which an infectious agent may be transferred directly or indirectly from an infected person to another person. Infectiousness may occur before onset of disease and for some infections this time period may be considerable, as may be the variation in level of infectiousness during the course of the infectious period. In this review, very limited information of infectiousness was found (only some data for varicella).

Pathogen shedding and infectiousness are closely related, so for some diseases infectiousness may perhaps be inferred from data on shedding of the infectious agent. Laboratory methods may influence the estimate of shedding duration and its applicability to provide information on period of infectiousness (see 'Diagnostic tools').

### **Duration of shedding**

The duration of shedding is the period during which a patient excretes the organism (time from the onset of clinical disease). For a good interpretation of a published duration, it is important that authors provide good definitions. In this review, included cases are by definition symptomatic, meaning that in most included studies the onset of symptoms will be the start of measurement. Calculation methods may influence the estimate of shedding duration. For example, shedding period can be measured as the time between (and including) the day of a specified symptom, until (and including) the last positive sample, first negative sample or midpoint between last positive and first negative; information on sampling frequency and sampling duration (e.g., until two negative samples) and missing data is also important in this matter. Munywoki et al. [182] present results for shedding duration intervals based on different ways of dealing with censoring. In their example in RSV patients, the median duration of shedding according to their minimum estimate was six days less than the median duration according to their maximum estimate. It is obvious that infrequent sampling would increase the difference between these estimates. As another illustration, George et al. [183] have shown, more than half a century ago, how assumptions regarding when a patient becomes negative (first negative after last recorded positive results vs. week preceding first of a series of negative results after being positive) can affect the results. In their example with patients with paratyphoid fever, the difference between outcomes using these two definitions was usually relatively small, although at some points in the study it was substantial. The same was illustrated by Nelson et al. [81]. In their trial, the number of days of *Salmonella* shedding until the first of at least two negative cultures (1–111 days, mean  $\pm$  SEM: 28.5 d  $\pm$  9.4; median: 12 d) was considerably larger than that until the last positive culture (177 days, mean  $\pm$  SEM: 20.9 days  $\pm$  6.8 d; median: 11 d), although the medians do not differ that much.

Unfortunately, shedding is not often the main variable of interest of a study. Hence, measurement is often poorly defined or not accurately performed (e.g. irregularly, infrequently). It may be a main outcome in some RCT's, and then sampling will be sufficiently frequent; however, in these studies shedding is often:

- not measured long enough, as the goal is to compare shedding values among groups with different treatments at a comparable time point in the study (not necessarily until all patients have stopped shedding)
- not measured from the onset of symptoms, but from a later time point (e.g., when the patient was hospitalized or enrolled in a study), leading to an underestimation of the duration of shedding compared to measurements that start at symptom onset.

Sometimes proportions or percentages of patients positive over time were reported. However, the number of patients sampled often decreased over time, and if the sampling strategy was not clearly defined, it is not impossible that patients were no longer sampled once they were found to be negative. The % positive per time point among those sampled could therefore be biased by containing relatively more people who are shedding for longer. In most studies, both a clinical diagnosis and laboratory confirmation are required for case ascertainment. However, there is always the possibility that cases were correctly clinically diagnosed but cleared themselves of infection before specimens were obtained [183]. If in that case they were not included as case in the study, this could have led to an underestimation of the number of individuals with short duration of shedding. When sampling appeared highly inadequate, a study was excluded from the review. However, this was a rather grey area; some studies that sampled only once or twice, but had large samples or other specific circumstances, were still included.

In addition to timing issues, the start of symptoms may be misclassified because of inaccurate patient recall.

### **Population characteristics**

Characteristics of the study population that may influence the outcomes are amongst others age, treatment (medication or vaccination), or the occurrence/inclusion of asymptomatic infections.

Age: child vs. adult, older child vs. younger child

Focus of the search was scientific information addressing children only or with clear age strata (a small % of adults in the population was sometimes accepted, e.g. if staff at schools or daycare centres were included). For two reasons we did not include data on adults.



The search was aimed at the population from 1 month until 18 years and thus articles on adults were not obtained systematically, and, more importantly, at least for the following agents there are indications that our parameters of interest change with age, for example longer shedding with younger age: RSV [182], *E. coli* [65, 71], influenza [184], *Salmonella* [185], norovirus [34].

An example of modification of shedding by age is found in the study by Ng et al. [184]. In this study, duration of shedding of influenza (both A and B) was assessed in outpatients in 45 public and private clinics in Hong Kong during February to September 2007 and January to September 2008. In total, 294 patients (43.2% male) that did not receive antivirals were included: 47 (16.0%)  $\leq 5$  years, 127 (43.2%) 6–12 years, 27 (9.2%) 13–17 years and 93 (31.6%)  $\geq 18$  yrs old. A group prescribed oseltamivir treatment ( $n=90$ ) was also included, as the aim of the study was to assess the indirect effectiveness of oseltamivir in reducing secondary household transmission. Nose and throat swabs were collected and tested for influenza by viral culture (2007) or reverse-transcription polymerase chain reaction (2008). Patients were followed-up for seven (2007) or ten (2008) days, in which two or three additional tests were performed. Duration of shedding was defined as the period from symptom onset until cessation of viral shedding and the latter was defined as the interval between the last positive laboratory result and the first negative laboratory result. The time from symptom onset to cessation of viral shedding was analysed using regression models allowing for the interval censoring. Explanatory variables included oseltamivir use, age, sex, vaccination history, baseline symptom score and type of influenza virus. Analyses were stratified by year to allow for potential differences in duration of shedding detected by culture (2007) and RT-PCR (2008). In a model correcting for all other variables, children statistically significantly shed virus for 40–80% longer than adults, depending on their age and year of the study. Thus, the overall estimation of duration of shedding is not eligible for this review.

To include data on adults, it first needs to become clear for which parameter and which disease/agent the data can be extrapolated to children in a valid way (from studies with sufficient power; studies using multivariable statistical modelling can be helpful in this). The age threshold for classification as a child or adult should be clearly defined. Otherwise, the safest way to gain valid data is to include children only. As older and younger children may also differ, age needs to be reported and data stratified as much as possible.

### Treatment

As for the above, there are indications from the literature that the parameters in the review change with either preventive or curative treatment. For example, use of antivirals may decrease duration of infectiousness and shedding in influenza (and hence limit the spread of disease), although there is some controversy about this notion. Median shedding duration of *E. Coli* O104:H4 was significantly shorter in patients with antibiotics treatment than in those without [71]. Use of antibiotics and antimotility agents is assumed to worsen the (clinical) course of *E. coli* O157 infection [186], and may therefore also influence the period of infectiousness or shedding. For this review, any available information on treatment of a study population has been extracted into the evidence tables. A limitation is that this information was not always presented in the publications.

To include data from treated patients, it first needs to become clear for which parameter and which disease/agent these data can be used in a valid way (from studies with sufficient power to detect a difference between treated and untreated; studies using multivariable statistical modelling can be helpful in this). For interpretation of findings it is important for authors to record the date or day with respect to symptom onset of the therapy onset of that no therapy was administered.

### Asymptomatic infections

In practice, the majority of cases will only be discovered after they present with symptoms (unless there is reason to instigate an outbreak investigation). There are indications from the literature that the parameters in the review change with symptomatic or asymptomatic infections. An example of this can be found in the study Van et al. [22] and in the study by Munywoki et al. [182]. In the latter study, duration of shedding of respiratory syncytial virus (RSV) was assessed in infants and their household members in rural coastal Kenya in the RSV season of 2009–2010. In total, 179 subjects (53.6% female) having 205 episodes were included, with a median age at start of first observed infection of 6.5 years (IQR 2.4–14.5). Of these 205 episodes 87 were asymptomatic. Nasopharyngeal samples were collected twice each week and tested by real-time multiplex polymerase chain reaction. The rate of recovery from RSV infection was lower by 44% (i.e. shedding duration increased) in symptomatic infections (118/205) relative to asymptomatic infections (adjusted HR 0.56, 95% CI 0.40–0.79).

To include data from subjects with asymptomatic infections, it first needs to become clear for which parameter and which disease/agent data from asymptomatic cases can be used in a valid way (from studies with sufficient power to detect a difference between symptomatics and asymptomatics; studies using statistical multivariable modelling can be helpful in this).

## Diagnostic tools

The parameters in this review may be influenced by the lab-techniques that are used to measure them, i.e. their validity, sensitivity, specificity, limits of detection etc. The applied diagnostic tools may influence the exact estimation of duration, their applicability to give information on the period of infectiousness, and whether a case is confirmed as a case or not. The influence will probably be greater for the older studies, since detection methods have been optimised over time.

An example of consequences for estimation of the period of infectiousness is the shorter duration of virus excretion as measured by viral culture for all influenza types as compared to measurement by Reverse transcription polymerase chain reaction (RT-PCR) [184, 187]. For norovirus, PCR assays may be used to detect viral Ribonucleic acid (RNA) during extended excretion of Norovirus, but as these cannot discriminate viable and non-viable viruses, it cannot be determined whether the virus is infectious and capable of transmitting infection (in the case of norovirus it is the only option, as it cannot be cultured) [32]. A difference has also been shown between the results of measurement of norovirus shedding duration using enzyme immunoassay or using RT-PCR [46].

Other issues are sampling specimens and the availability of routine testing methods. For example, detection of *E. coli* O157:H7 requires specific testing that is not performed in routine stool cultures. This implies that studies or screening needs to aim at this pathogen specifically for identifying cases [186]. Kumar et al (2012) [188] showed that for typhoid fever detection, analyses of blood and stool samples were inferior to urine sample analysis in sensitivity, with detection rates of 90.9% and 68.1%, respectively. Culture isolation was observed to display very poor sensitivity (31.8%). Therefore, studies that based typhoid case detection on blood or stool samples may show differing results for incubation period or shedding.

Information on lab methods were collected, but information on reproducibility and validity was not collected in this review; a future project may add this information.

## Study design and methodology

The design of included studies may have influenced the values for parameters summarised in this review, which should be taken into account when interpreting the results. For example, observational studies such as outbreak investigations have increased susceptibility to recall bias. Also, the setting (e.g., household, school, hospital) in which cases were studied may play a role. The time between two successive cases may be different in different settings such as school, community or household, e.g. because of differences in closeness and duration of contacts. Given that close contact should facilitate transmission during the early phase of an infectious period and that incubation periods of some infections may be negatively associated with infectious dose, one might expect case-to-case intervals in households to be shorter than those observed in extra domestic circumstances [189]. Household studies permit identification and measurement of presymptomatic shedding and clinical symptoms of secondary cases can be described without surveillance bias if secondary household cases are identified through serial testing. For secondary cases it must be ascertained that they result from the primary cases and not from other cases in the community/institution; also it must be ascertained that secondary cases are not tertiary cases; both incorrect assumptions would lead to incorrect estimation of the parameters in this review.

Not all studies take confounding or modifying factors, such as age, treatment, infectious dose or contact patterns into account; if they do, often a stratified analysis is performed. Stratified analysis has the advantage that the actual values for the groups to be compared (including the range) can be reported. However, it decreases power to detect a difference, especially when stratifying on more than one factor, e.g. age and treatment (although combined stratification is hardly ever presented). Multivariable modelling has more power to detect differences, can include several influencing factors and can differentiate between modifying factors and confounding factors.

In conclusion, the influence of study design characteristics needs to be taken into account when interpreting the results.

## Exclusion period

### Isolation of cases and settings

Although the focus of this review was on isolation of (symptomatic) cases, most commonly studied was isolation/closure of schools (mostly on influenza). There was a lack of studies comparing exclusion periods in cases and presenting a measure of effectiveness. Roggendorf et al. [190] state that immediate exclusion of children without measles vaccination or naturally acquired immunity from classes for two weeks helped to prevent the spread of the virus, but this is not quantified and the study does not compare to a situation without exclusion (control group) or other exclusion period. Some studies cannot present conclusive evidence on exclusion, because multiple interventions were evaluated at once, e.g. by Chorba et al. [191]. Considering the scarcity in 'real-life' scientific studies addressing the effectiveness of exclusion periods, simulation studies could provide valuable insights.



## Recommendations on exclusion period

Many handbooks exist and many national and international institutions develop exclusion tables. The information sources on incubation times/period of infectiousness underlying these recommendations are often not stated. The main sources we used to summarise current recommendations (Table 5.3) were:

- the CDC website
- the WHO website
- the American Association of Pediatrics Red Book [113] (and also from AAP, Managing diseases in childcare and schools. A quick reference guide. 2nd Edition [114])
- the review by Richardson et al. from 2001 [115], which could not be included as peer-reviewed literature as it did not provide population and study characteristics and it contained ineligible publication types (opinions and clinical experience of experts not supported by published data, and sample size <5). However, it provided useful information and recommendations were developed based on the collected data.

In addition, for some diseases/agents they judged exclusion not to be effective or not required. Exclusion was not deemed effective because:

- infectiousness occurred before symptoms, for the following diseases/agents: chickenpox, fifth disease, hepatitis A, measles, meningococcal disease, rubella, fifth disease, mumps, paratyphoid fever, rubella.
- asymptomatic cases contribute to transmission, for the following diseases/agents: enterovirus infections, hepatitis A, infectious mononucleosis, meningococcal disease, mumps, paratyphoid fever, pertussis, roseola infantum, rubella, scarlet fever, shigellosis, streptococcal pharyngitis, typhoid fever.

Exclusion was not deemed necessary due to mildness of symptoms, for the following diseases/agents:

- enterovirus infections, Fifth disease, hepatitis A, influenza A, roseola infantum, streptococcal pharyngitis.

Sustainability and acceptability of control measures is an important aspect to consider when formulating guidance and evaluating its impact [65]. In the recent study by Dabke et al. [65]; VTEC in childcare facilities, children were excluded until two consecutive faecal specimens - collected after resolution of symptoms and at least 24 hours apart - were culture negative. Median duration of exclusion was 39.5 days. In 30% of cases there was difficulty in implementing the exclusion period. Reported reasons were: parental anxiety and/or communication issues, disruption to family and social isolation, issues with sampling (delays and loss), financial issues and childcare issues. Transmission appears to be low. The authors propose that supervised return of prolonged shedders to childcare facilities could be considered if evidence of low transmission is confirmed.

Another aspect to consider is who has the highest risk in the surroundings of the child, e.g. when younger siblings or pregnant mothers (at home) have high risk of complications. This review did not address case contacts.

When recommending exclusion periods, relevant modifying influences may be stratified upon, e.g. age or treatment.

## Other data sources

In addition to the systematic review of peer-reviewed scientific literature, a number of other data sources have been searched for relevant information. This 'grey' or 'other' literature may be of value with the development of guidance on exclusion and other control strategies, since peer-reviewed data on the required outcomes appeared to be limited. Although some governments publish (part of) their infectious disease related information in ways that can be identified by PubMed or Embase, e.g. UK and Australia, this is not the case for a large number of other countries.

It has to be noted however, that data found for incubation period, period of infectiousness or shedding, and exclusion period in the other data sources were often unsourced. Therefore, they should be interpreted with care.

It may be worthwhile to search data from national surveillance programs or other data by national health institutes that is not included in the PubMed or Embase databases.

## Limitations

This systematic literature search assessed the evidence on incubation period, period of infectiousness or shedding for a selected number of infectious diseases with the goal to quantify the minimum period required for school exclusion. The search was conducted in two phases. The first one, based on a single database (PubMed) yielded 3 426 studies, with a range of study populations, ranging in age composition, symptomatology, treatment, vaccination, diagnostic tools, viral load, study design and reporting of key definitions.

In order to increase the sensitivity of the literature review, a second search was performed with two databases (PubMed and Embase); this one used extended search strings and no limits (time limit, geographical limit and language limit). A total of 12 619 publications were identified, including dated papers in a wide range of languages that are not accessible in electronic format.

Thus, these papers were subjected to strict inclusion and exclusion criteria. The age of the study population was restricted to children and teenagers between 1 month and 18 years of age. The excluded population were neonates and adults since they were not the research focus of this review. Moreover, we also excluded children with a certain health status (underlying conditions, children under treatment or chemoprophylaxis, carrier status or vaccinated children) which could impact the period of infectiousness and shedding or incubation period and as such the days for exclusion.

Both observational and experimental studies were included in our search. The strengths and limitations of the individual study designs is discussed at length. One of the limitations of our systematic review lies in the fact that no standards on the effectiveness of public health interventions exist; thus no conclusions on the effectiveness of school exclusion can be drawn based on our findings. Another limitation is the fact that for certain diseases only a few or no studies exist at all. The grey literature will be consulted for the development of a guidance including guidelines from CDC and WHO.

## 5. Conclusions and next steps

This review specifically addressed incubation period, period of infectiousness/shedding and exclusion period, and may serve as a basic document for producing a guidance with the best available relevant scientific information based on the period of incubation, period of infectiousness and shedding.

The guidance will contain data on the most prevalent communicable diseases, as reviewed in this report, with the aim to assist the EU public health professionals working with school or other childcare setting and to facilitate their decision-making process on the suggested minimum leave for an infected person (1 month–18 years old) attending a school or other childcare setting for the period of communicability.

The information in this review may be extended by adding peer-reviewed data not originally in the inclusion criteria and may be combined with expert opinion and (seemingly) unsourced data.

Considering that many other aspects play a role in the decision for which diseases to exclude and for how long, such as severity of the disease, economic burden, feasibility and parental considerations, these conditions can be added to the methodological information when defining the minimum exclusion periods from school or other childcare setting.

Based on the available resources the systematic search will be revived in the coming years to determine whether all or part of it should be updated. Information on the progress of any update will be integrated in the document and posted on the ECDC website. The use of the document will be closely monitored during this interim period through stakeholders and the experience will be used to improve the revised version.

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