A rapid review update- case definitions for surveillance integrated for influenza and COVID-19

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Executive summary

The novel respiratory virus, SARS-CoV-2 emerged towards the end of 2019 and has affected the global human population. There have been a significant number of publications reporting the clinical features of COVID-19 (infection caused by SARS-CoV-2) ever since. However, given this is an emerging virus with several variants discovered, it is possible that the reported clinical presentations of COVID-19 may have changed over time. The Global Influenza Surveillance and Response System (GISRS) network has integrated the testing of COVID-19 specimens into the workflows during the COVID-19 pandemic. It is essential to know whether the commonly used case definitions for influenza surveillance (for example, influenza-like illness (ILI) and severe acute respiratory infection (SARI)) are appropriate for COVID-19 surveillance or whether they need to be modified for combined COVID-19 and influenza surveillance. This rapid review update aims to synthesise the existing evidence on case definitions used to incorporate COVID-19 into influenza surveillance. This review is conducted in two parts, clinical characteristics of COVID-19 and the performance of current surveillance for COVID-19 and influenza.

This review shows that fever and cough continue to be the commonest clinical features for COVID-19 across all age groups. For all age groups, except children, other features included loss of taste or smell, fatigue, loss of appetite, shortness of breath, hypoxia, and expectoration. Though fever and cough were the most prevalent features for children, headache and nasal congestion were more common in children than in adults or all ages combined. For COVID-19 surveillance, ILI, SARI and acute respiratory illness (ARI) were the commonly used case definitions. We did not find any studies conducting a formal assessment of the performance of these case definitions for capturing COVID-19 cases. Even so, several studies demonstrated that the rise in incidence rates of ILI/ SARI/ARI was higher during the pandemic period compared to earlier seasons, and these excess cases very often matched with the geographical locations and age groups most affected by COVID-19. This finding is suggestive of COVID-19 cases successfully being captured by the influenza surveillance systems.

Contents

Section 1- INTRODUCTION

In November 2020, the WHO produced interim guidance on the adaptation of the Global Influenza Surveillance and Response System (GIRS) to help maintain influenza surveillance in addition to monitoring SARS-CoV-2[1]. The report provided guidance on managing the disruptions to influenza sentinel surveillance and implementation of surveillance of COVID-19, advising combined testing for influenza and SARS-CoV2. Through these means, it was hoped that surveillance would capture changes in seasonality of influenza due to circulation of both viruses and detect co-infection with SARS-CoV-2 and influenza or other respiratory viruses.

Data available at that time suggested the case definitions used for influenza surveillance may also capture COVID-19, with sensitivity and specificity for influenza-like illness (ILI), acute respiratory illness (ARI) and severe acute respiratory illness (SARI) being similar across both viral infections[1]. In parallel with this, a literature review was conducted to examine the performance of case definitions for influenza surveillance in identifying SARS-CoV-2. Despite no studies reporting sensitivity or specificity for case definitions, three studies using ILI/ARI or SARI found SARS-CoV2 positivity between 1.8 - 25.6%, and other studies reported correlations of excess ILI/ARI/SARI cases with COVID-19[2]. To support the development of a case definition for the interim guidance, the literature review also reported the clinical features of COVID-19. Using available literature up to 18th August 2020, clinical features were ranked in order of median prevalence. Fever was the commonest (83%), followed by cough (60%), loss of taste or smell (41%), fatigue (31%) and loss of appetite (30%). Other features recorded occurred in 12% or fewer cases. For GIRS to continue to be effective at both influenza and SARS-CoV-2 surveillance, it is critical to update guidance using the current data and up to date literature.

This report aims to assess whether a year on, studies have noted any change in clinical features of COVID-19 and whether studies have assessed the performance of case definitions used in influenza surveillance for detection of COVID-19. Therefore, this literature review is split into two sections: the first section synthesises the evidence from systematic reviews on clinical features of COVID-19; the second section examines the use of case definition for COVID-19 in influenza surveillance, with particular focus on the inclusion of performance metrics by studies (e.g., sensitivity and specificity).

Section 2- CLINICAL CHARACTERISTICS OF COVID-19

Methods

Data source

Given that this was a rapid review, we focused solely on existing systematic reviews on the clinical characteristics of COVID-19. We extracted reviews from the collection of "clinical characteristics" indexed by the "COVID-19 evidence review" website.[3] As we could not search the database by entry date directly, we used Dataminer (https://dataminer.io/) to extract the information to retrieve the entry date of each record. We downloaded the records into Microsoft Excel where we extracted the items that met our entry date criteria and then uploaded them into EndNote. The reviews were screened according to the eligibility criteria below.

Inclusion criteria

- Systematic review/rapid review that reported clinical features of polymerase chain reaction (PCR) or rapid diagnostic test (RDT) confirmed COVID-19 infection within the general population; AND
- Systematic reviews reporting the pooled estimate of the prevalence of clinical characteristics; AND
- Reviews added to the database from 19th August 2020 to 19th August 2021.

Exclusion criteria

- Reviews not reporting a pooled estimate for clinical features or reporting non-specific clinical symptoms (e.g., gastrointestinal manifestations); OR
- Reviews not limiting their study population to PCR or RDT confirmed COVID-19 cases, OR
- Reviews focussing on sub-groups or patients with special medical conditions (e.g., patients with comorbidities, pregnant women, etc.); OR
- Non-systematic or narrative reviews; OR
- Reviews that focused on particular syndromes that may be a sequelae of COVID-19 (e.g., Multisystem inflammatory syndrome in children (MIS-C), Guillain-Barre syndrome and acute respiratory distress syndrome); OR
- Studies published in languages other than English

Selection and extraction

The title and abstracts and full texts of all the identified reviews were screened independently by two reviewers on COVIDENCE[4]. We resolved any conflicts by discussion between team members. An Excel spreadsheet template was designed for data extraction. The following general information was collected from each review: last date of literature search, country, age group and severity. For each clinical feature, we collected the point estimate and the corresponding 95% confidence intervals (CI) of pooled estimate of prevalence; we also collected the number of studies and subjects involved in that estimate. We extracted the estimates separately by age groups such as adults or children, as specified in the review. Clinical features that were either non-specific or included multiple features within them (e.g., gastrointestinal symptoms) were excluded from data analysis; however, prevalence of asymptomatic cases was included.

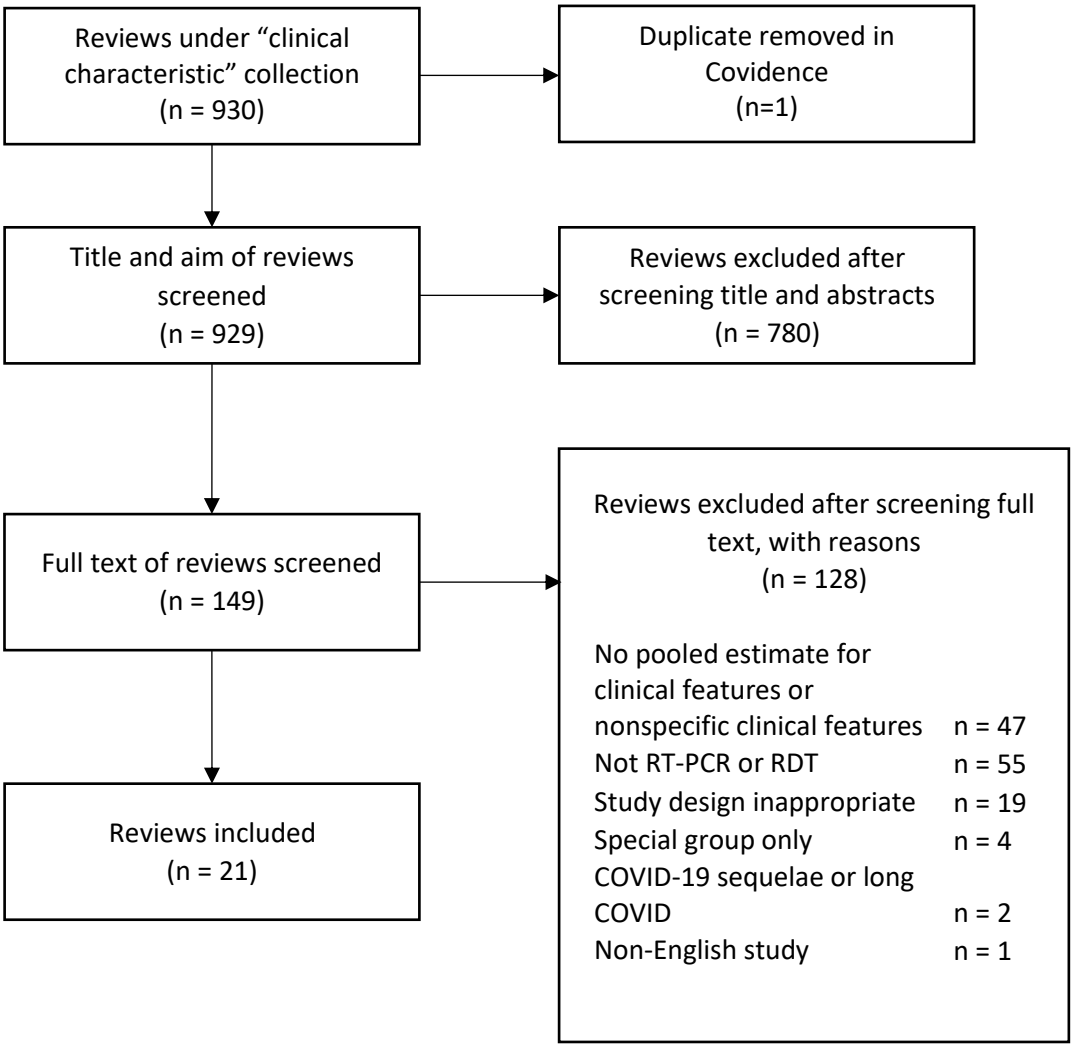
Data analysis

We calculated the median and interquartile range (IQR) of the point estimates for each symptom for the pooled prevalence reported by the reviews. Clinical features were ordered by their median

prevalence. The reviews were combined by all ages with subsequent analyses undertaken for reviews that specified children or adults only. We noted that some reviews included multiple features, whereas others only specified a few. It is possible for bias to occur if studies purposely identified specific symptoms compared to those reporting all or multiple features. To reduce bias when ranking most prevalent clinical features, we undertook sensitivity analysis to include only reviews with five or more clinical features and compared this to the main analysis. In addition, another potential source of bias could be the inclusion of the same primary study several times within the included reviews. Therefore, we undertook another sensitivity analysis to compare the ranking of features obtained in the main analysis, to the ranking obtained by selecting only the most recent review (as indicated by the last date of search) for each symptom. All data analyses and visualisation were conducted using R software (version 4.1.1).

Results

Figure 2.1: PRISMA flow chart for flow of studies



Characteristics of included reviews

Of 930 reviews identified, 149 proceeded to the full-text screening stage. Out of these, 21 reviews were deemed eligible for data extraction[5-25]. Nineteen had global coverage, with one restricted to

studies from Asia and the Pacific[24] and one to China alone[25]. The combined reviews covered all ages and reported 26 clinical features. Four reviews[9,12,16,24] restricted their study population to adults alone, identifying 24 features whilst the five reviews[8,10,11,13,23] restricted to children alone reported only thirteen clinical features.

Prevalence of symptoms

For all reviews combined, fever and cough were the two most common symptoms of COVID-19, with their median prevalence being 76% (IQR: 58 – 80) and 59% (IQR: 45 – 63), respectively. These two symptoms were followed by loss of taste or smell (42%, IQR: 32 – 50), fatigue (39%, IQR: 22 – 44), hypoxemia (33%, IQR: 33 - 33), shortness of breath (27%, IQR: 19 - 30) and loss of appetite (18%, IQR: 14-34), with asymptomatic cases accounting for 25% (IQR: 17 – 37). All features are shown in figure 2.2. Likewise, fever and cough had the highest prevalence for adults and children alone. Fever was found in 78% (IQR: 64 – 80) of adults and 58% (IQR: 54 – 65) of children, and cough was found in 59% [IQR: 52 – 61] of adults and 43% [IQR: 42- 45] of children. The pattern of symptoms following this differed in comparison to all ages combined. For adults (n=4 reviews, shown in figure 2.3), hypoxemia (33%, IQR: 33- 33) had a higher prevalence than the loss of taste or smell (25%, IQR: 13-23); however, hypoxaemia was only reported in one study[16]. The other features in adults had similar prevalence rates to those reported for all ages, with shortness of breath (27%, IQR: 23 – 28), fatigue (26%, IQR: 17 – 32) and expectoration (23%, IQR:23 – 24) being seen in above 20% of adult cases. However, the ranking of these clinical features was different in adults compared to all ages. In contrast, for children (n =5 reviews, shown in figure 2.4), headache (34%, IQR: 18 – 51) and nasal congestion (20%, IQR: 20 – 20) were the third and fourth commonest features, followed by muscle pain (20%, IQR: 12 – 27). Though these were present for adults and all ages, they were reported less often in these populations. Like all ages, asymptomatic cases were estimated to be above 20%, occurring in 23% of cases in children (IQR: 19 – 29%). For adult only, asymptomatic cases were estimated to be lower at 17% (IQR: 10 – 24%) though the range could extend to 24%.

To provide a comparison between the 2020 review[2] and this review, we were able to describe the top features found in both reviews for all ages. Fever and cough ranked the highest, followed by loss of taste or smell and fatigue for both reviews. Other features less commonly reported in the reviews were loss of appetite, expectoration, and shortness of breath. However, these comparisons need to be interpreted with caution as there are differences between the present review and the one conducted in 2020, which prevents direct comparison of the order of ranked symptoms, notably the grouping of clinical features and variation in the reported clinical features. Furthermore, there are likely variations in the underlying populations, circulation of SARS-CoV-2 variants, and possible publication bias with studies choosing to highlight uncommon features.

Sensitivity analyses by latest search date and reviews with multiple clinical features

Fever and cough were still the most prevalent symptoms in all ages and in adults using only the most recent review (see figures S1-S3 in appendix 2.3) and in studies with five or more clinical features (see figures S4-S6 in appendix 2.3). Though the order of subsequent features was changed; hypoxia, shortness of breath, expectoration, fatigue, loss of appetite, and asymptomatic still featured within the more prevalent symptoms. Loss of taste and smell was within this set of prevalent symptoms for all ages but fell to the least common in adults by the most recent review. When examining features in adults by reviews with multiple features the prevalence of loss of taste and smell increased to being within the commoner features. Therefore, the previous fall was thought to related to only one review[16] . For children, fever and cough were the most prevalent features by reviews with multiple clinical features, whereas headaches became the commonest for most recent search.

Figure 2.2: Box and whisker plot showing median prevalence of symptoms for all ages

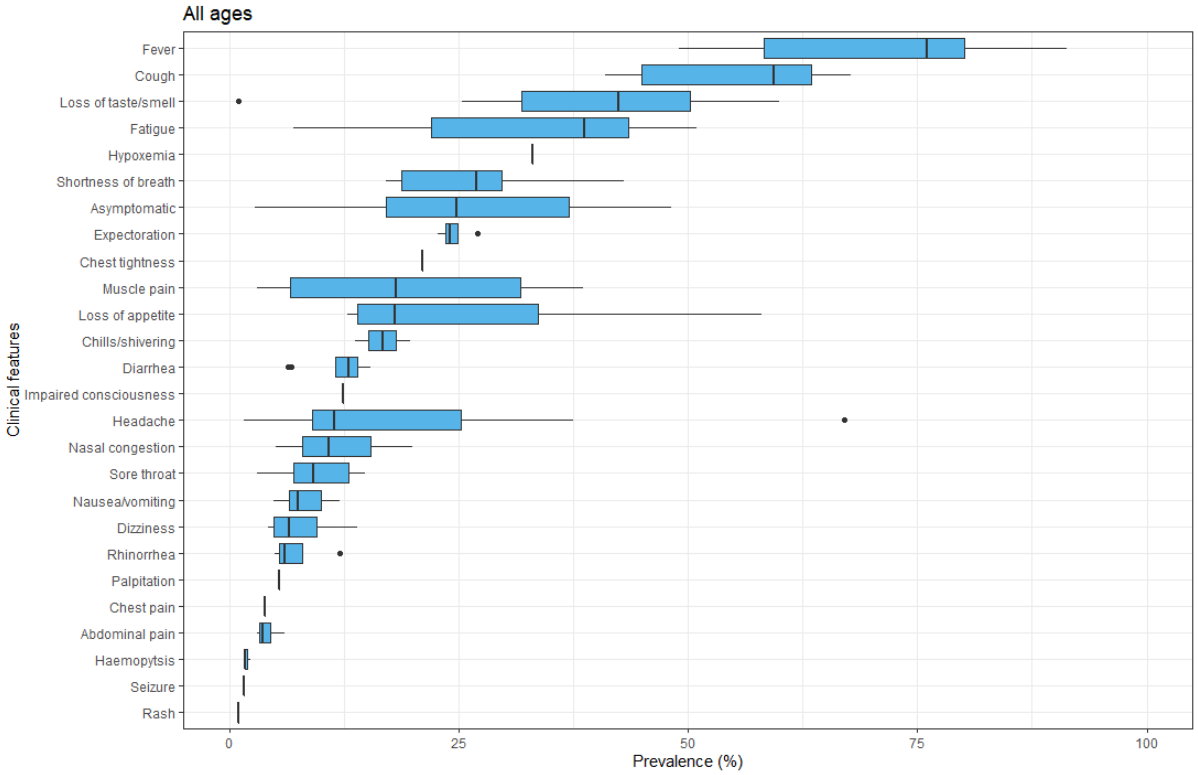


Figure 2.3: Box and whisker plot showing median prevalence of symptoms for adults

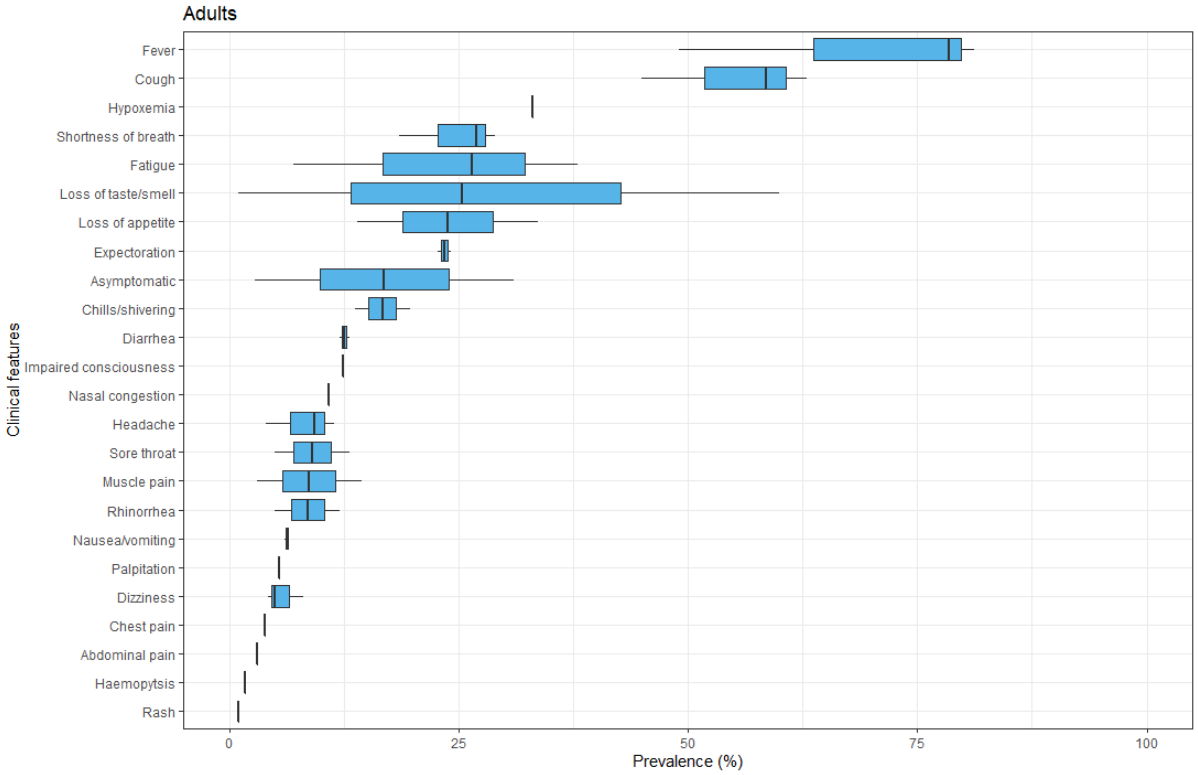
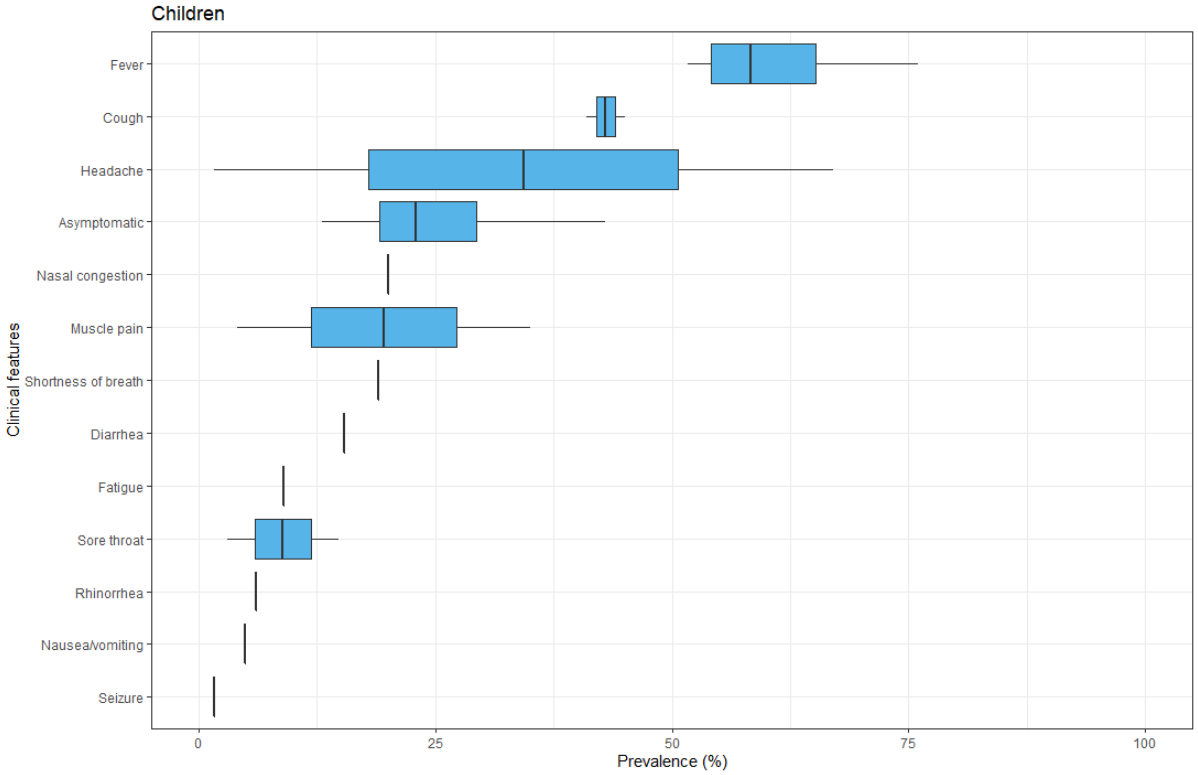


Figure 2.4: Box and whisker plot showing median prevalence of symptoms for children



Limitations

Asymptomatic cases were reported as 25% for all ages. The information we have included from reviews on asymptomatic cases did not differentiate presymptomatic and asymptomatic. Therefore, we are not able to comment if those asymptomatic cases went on to develop symptoms. As this is an umbrella review (a review of systematic reviews), recent primary studies published since this time might not be included in a systematic review given that the latest search date for the included reviews was in November 2020. Also, we might miss systemic reviews published after our search date (19th August 2021). In addition, other limitations include lack of formal quality assessment of reviews, lack of information on the variation of clinical features by variants and a small number of reviews on adults alone and children alone. Lastly, we have pooled results of prevalence which have been estimated in specific unknown subpopulations (e.g., only hospitalised cases).

Conclusions

Fever and cough were the most common clinical features for all ages and for adults and children separately. This result was in line with the 2020 review of clinical features. Other prevalent features for all ages and adults included loss of taste or smell, fatigue, loss of appetite, shortness of breath, hypoxia, and expectoration. Children may present with different features as headache and nasal congestion were more common in this group; however, this was only based on five reviews.

Section 3- PERFORMANCE OF COVID-19 SURVEILLANCE BASED ON EXISTING FLU SURVEILLANCE

Methods

Data source

We searched the WHO database of global COVID-19 literature on 29th August 2021. We developed two different search strategies, namely strategy A and strategy B, which focused on capturing different aspects of research. Strategy A focused on case definitions that were used by countries for surveillance of influenza and COVID-19 concurrently and did not contain any terms on the performance of the surveillance (for example, sensitivity and specificity) whereas strategy B focused on the performance metrics of the surveillance. Details of the two strategies are provided in appendix 3.1.

Inclusion criteria

- Studies using influenza surveillance to monitor COVID-19 activity; AND
- Studies specifying case definitions used for surveillance testing

Exclusion criteria

- Study population not under influenza surveillance; OR
- No description of case definition used, OR
- No assessment of number of COVID-19 cases; OR
- English translation or full text unavailable

Selection and extraction

We conducted a search by combining the two strategies with the OR operator. The retrieved results were de-duplicated in Endnote and ASySD (https://camarades.shinyapps.io/RDedup/) before undergoing screening. All papers were screened by two reviewers for both title and abstract, and subsequent full-text screening. The screening process was undertaken on COVIDENCE[4]. Any disagreements were resolved by discussion amongst team members. An Excel spreadsheet template was designed for data extraction. Information was collected on location and country, study period, sample size, case definition used, method, main findings, and interpretations of findings relevant to COVID-19 surveillance.

Data synthesis

We synthesised the available data narratively. We presented the results under three headings based on the study aims; (1) studies describing case definitions used without evaluating their performance in capturing COVID-19 cases; (2) studies alluding to the performance of the case definitions by reporting correlations with COVID-19 cases from other sources; (3) studies reporting use of ILI laboratory surveillance for capturing COVID-19 cases.

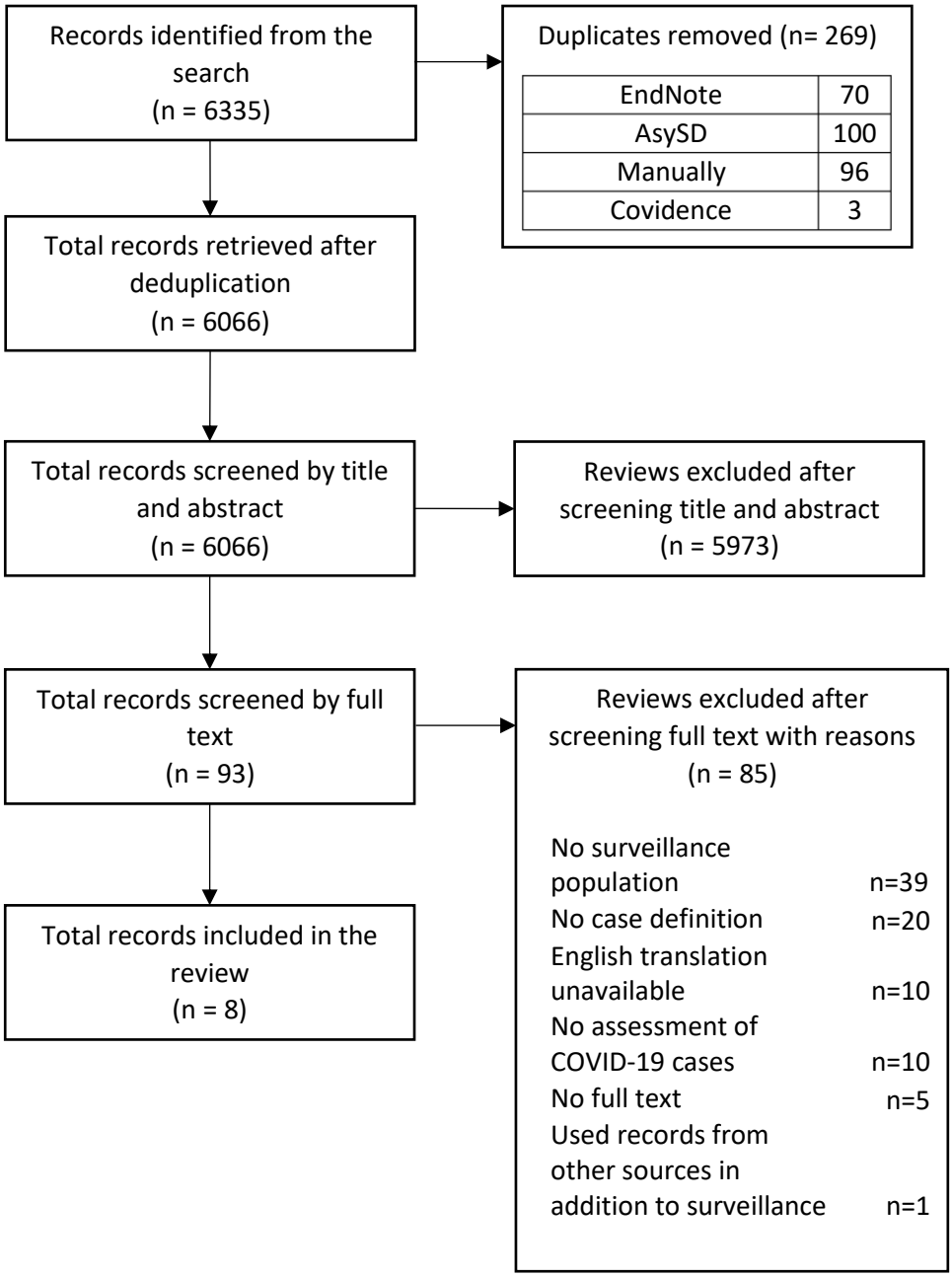
Results

We screened 6066 titles and abstracts. Of these, 93 studies were deemed eligible for full text screening. A total of eight records were included in this rapid review (Figure 3.1)[26-33]. Full text studies/reports were available for seven records and one record was available only as an abstract.

The studies were conducted in Germany[26], Italy[27,29-30], Belgium[28], , Spain[31], India [32] and United Kingdom[33].The data from the pre-pandemic era ranged from 2015 to 2019 and that from the COVID-

19 period ranged from 2019 to 2021. The findings are summarised in Table 3.1. We did not identify any studies formally evaluating the performance of existing influenza surveillance systems in capturing COVID-19 cases (i.e., reporting sensitivity or specificity).

Figure 3.1: PRISMA flow chart for flow of studies



Studies describing case definitions without evaluation of performance

Three studies described case definition without evaluating its performance. One hospital based study [32] conducted in India, used a modified severe acute respiratory illness (SARI) case definition of 'febrile respiratory symptoms, OR radiographic evidence of pneumonia, OR acute respiratory

distress syndrome of ≤14 days duration, AND need for hospitalisation; in the absence of an alternative aetiology that fully explains the illness'. The study's authors recommended that including chest radiography into the WHO SARI definition might improve COVID-19 surveillance in hospital settings. Over forty percent (44.8%) of the patients presenting to the Emergency department (ED) of the hospital had confirmed SARI infection and mortality was high in COVID-19 as well as non-COVID-19 cases. However, COVID-19 cases required longer hospitalisation. It must be noted that this was a single centre study with a small sample size (n= 212). Another retrospective study from Belgium analysed National Influenza surveillance network data[28]. The combined definition for influenza-like illness (ILI) and SARI that was used by the authors was 'acute respiratory illness with onset within the past 10 days, with measured OR reported fever of 38°C OR greater, cough, OR dyspnoea, OR a combination of these symptoms, AND hospital admission for at least one night for the patients admitted to hospital'. This method successfully detected the first SARS-CoV-2 positive sample associated with the first COVID-19 case without travel history. Further, the prevalence of SARS-CoV-2 positivity increased between weeks 10 to 13 (from 1.3% to 52.9%) in hospital samples and between weeks 11 and 12 (from 18.2% to 27.3%) in primary care samples. The last study conducted in Valencia, Spain suggested that the European Centre for Disease Prevention and Control (ECDC) case definition can be extended for COVID-19 surveillance and for surveillance of any newly emerging pathogen in the future[31]. However, the samples in this study were collected very early in the pandemic period (November 2019 to mid-March 2020) and only one positive case of SARS-CoV-2 was detected.

Studies evaluating case definition performance by correlation with COVID-19 cases reported from other sources

Three European studies considered the performance of case definitions using other sources of data for COVID-19 cases. Two were reported from the Lombardy region of Italy[27,30]. The ILI incidence rates had reduced in the 2017-2018 and 2018-2019 seasons compared to earlier years but had increased in the 2019-2020. This rise was attributed to COVID-19 as the excess ILI cases corresponded to the reports of COVID-19 cases in the region by age group[30], geographical location[27,30], and COVID-19 test results[30]. The ECDC ILI case definition was used in one of the studies [30]. The exact ILI case definition used was unclear in the other study and it was only available as an abstract[27]. In the United Kingdom, the fall in GP ILI (using ECDC ILI case definition) consultation rates during the pandemic resulted in a reduction in the total number of cases under surveillance[33]. However, the all-cause mortality for all ages in the 2019-2020 influenza season was higher compared to earlier seasons. This excess mortality was in line with increase in deaths related to the COVID-19 pandemic. The final large study (n= 13,72,958) from Germany used case definitions for ARI, SARI, ILI, and respiratory syncytial virus (RSV) based on a combination of ICD-10 codes[26]. An unusually higher proportion of SARI amongst ARI cases detected by syndromic surveillance at emergency departments (ED) during the pandemic, was believed to be from SARI caused by SARS-CoV-2. This was notably observed during the five-week period in April 2020 to May 2020 (the peak being 17.1% in week 18 of 2020) and November 2020 to January 2021 (the peak being 14.2% in week 53 of 2020). The authors concluded that implementation of the influenza surveillance system is effective in detecting COVID-19 cases and likely to be a valuable tool for early detection of SARS-CoV-2 cases.

Studies using ILI laboratory surveillance for capturing COVID-19 cases

One study used the ECDC ILI case definition for ILI laboratory surveillance[29]. They found 10% positivity for SARS-CoV-2 and laboratory-based surveillance was said to be essential and effective for the detection of COVID-19 cases that might, otherwise, be missed. However, it should be noted that the sample size of the study was small.

Table 3.1: Summary of findings

First author, Year	Location (Study period)	Case Definitions	Descriptions of Case Definitions	Surveillance Method	Sample Size	Main findings and authors conclusions (in relevance to COVID-19 surveillance)
Boender, 2021[26]	Germany (March 2017 to March 2021)	*ARI	ICD-10 Code: [2,3,4]J00-J22, [5]J44.0, [6]B34.9, [8]U07.1, [9]U07.2	Syndromic surveillance data of ED attendance saved on the Robert Koch Institute server for acute respiratory infections (ARI) was used. Case definitions were based on combinations of ICD-10 codes	13,72,958	• The fall and winter of 2020/2021 season observed an absence of a flu season. • Emergency department attendance/ detection of ARI, SARI, ILI, and RSV decreased in March 2020 and during resurgence in September 2020, however, there was an increase in cases identified as SARI within ARI cases from April - May 2020 and November 2020 to January 2021 • The median proportion of SARI cases was 6.9% (IQR: 5.3 to 8.3) from 2017 to 2019 and only occasionally exceeded 10% and that was only in single weeks before the pandemic. During the pandemic, SARI proportion among ARI peaked twice for 5 consecutive weeks- week 15 (2020) to week 19 (2020) with a peak (17.1%) in week 18 (2020) and week 48 (2020) toweek 2(2021) with a peak (14.2%) in week 53 (2020). • SARI increase within ARI cases could indicate greater proportion of COVID-19 cases. The study concluded that syndromic surveillance ED (emergency department) data can help indicate trends in the pandemic, including severity of COVID-19, duration, timing, etc.
		**SARI	ICD-10 Code: [3,4]J09-J22, [8]U07.1, [9]U07.2			
		***ILI	ICD-10 Code (Probable case): [2]J06.-, [3]J12.8, [3]J12.9, [3]J18.-, [4]J22 ICD-10 Code (Confirmed case): [3]J09, [3]J10.-, [3]J11.-			
		****RSV	ICD-10 Code (Probable case): [3]J12.8, [3]J12.9, [3]J18.-, [4]J20.8, [4]J20.9, [4]J21.8, [4]J21.9, [4]J22 AND ≤ 2 years of age ICD-10 Code (Confirmed case): [3]J12.1, [4]J20.5, [4]J21.0, [7]B97.4			
Castrofino, 2021[27]	Lombardy, Italy (2017 to 2020)	***ILI	Not mentioned	National Influenza Surveillance System: Analysis of influenza surveillance system data by comparing ILI incidence rate distribution every week for the following influenza seasons: 2017-2018, 2018-2019, 2019-2020. Trends in data were used to identify coinciding abnormalities in ILI cases during the influenza seasons and the COVID-19 outbreak	Not available	• Three influenza seasons were compared. All three had similar patterns of ILI cases in the first 9 weeks of the flu season, after which the number of cases decreased in the first two seasons, In the 2019-2020 season, the number of ILI cases increased after the 9th week. Geographical locations of increase in ILI cases coincided with regions known to be the most greatly affected by COVID-19 • Implementation of the influenza surveillance system is effective in detecting cases to determine the state of the current pandemic situations and provides some insight on future complications during the pandemic with COVID-19 trends

First author, Year	Location (Study period)	Case Definitions	Descriptions of Case Definitions	Surveillance Method	Sample Size	Main findings and authors conclusions (in relevance to COVID-19 surveillance)
Fischer, 2021[28]	Belgium (2015 to 2020)	**SARI & ***ILI (Grouped)	Definition determined by study authors: acute respiratory illness with onset within the past 10 days, with measured or reported fever of 38°C or greater, cough, or dyspnoea, or a combination of these symptoms, and hospital admission for at least one night for the patients admitted to hospital	National influenza surveillance networks were retrospectively analysed. Respiratory specimens were collected from patients experiencing SARI or ILI, with ARI 10 days prior to specimen collection.	9067	• In early 2020, the Belgian SARI surveillance detected the first SARS-CoV-2-positive sample concomitantly with the first confirmed COVID-19 case with no travel history to China. • 73.3% of patients experiencing complications or who died had at least 1 potential risk factor for COVID-19. Prevalence of SARS-CoV-2-positive samples rose from 1·3% to 52·9% in weeks 10–13 in hospital samples and from 18·2% to 27·3% in weeks 11–12 in primary care samples. • The national influenza surveillance network is effective in SARS-CoV-2 surveillance and early detection of emerging coronaviruses.
Galli, 2021[29]	Lombardy, Italy (2019 to 2020)	***[1]ILI	ECDC	Sentinel laboratory-based surveillance and based on weekly sentinel physician reports on ILI and analysis of nasopharyngeal swabs	631	• No co-infections of SARS-CoV-2, RSV, or influenza viruses detected. Of the nasopharyngeal swabs collected, 31% tested positive for influenza viruses, 10% for SARS-CoV-2, and 7% for RSV. Influenza and RSV cases stopped/ decreased 7 weeks earlier than previous years, after which the only virus detected among ILI outpatients was SARS-CoV-2 • Laboratory based ILI surveillance networks are effective and essential for detection of SARS-CoV-2 cases that would otherwise be unidentified.
Grosso F, 2021[30]	Lombardy, Italy (2017 to 2020)	***[1]ILI	ECDC	Data on ILI from sentinel physicians' surveillance programme	2,18,696	• ILI incidence rate decreased in 2017-2018 (19%) and 2018-2019 (15%) season but increased in 2019-2020 season. • The link between the number of cases noted in 2019-2020 ILI surveillance and the number of COVID-19 cases noted is supported by the curve trends, the correspondence between age group, the correspondence by geographical locations and also by the COVID-19 test results (nasopharyngeal swab) • The influenza surveillance system is effective to identify COVID-19 at an early stage. It helps to detect SARS-Cov-2 among patients with ILI in a timely manner with high quality results
Iglesias, 2021[31]	Valencia, Spain (2018 to 2020)	***[1]ILI	ECDC	Data collected from Global Influenza Hospital Surveillance Network (GIHSN)	5176	• There was no evidence for COVID-19 infection in hospital admissions for ILI in Valencia before the pandemic (March 2020) • After re-testing 1,823 available samples that were collected between November 2019 and mid-March 2020 for SARS-CoV-2 (either positive or negative for seasonal viruses) only one SARS-CoV-2 positive was detected • Influenza surveillance networks are vigorous in identifying new respiratory viruses sharing the ILI /SARI symptomatology. This is important to extend the surveillance of COVID-19 and any new pathogens in the future

First author, Year	Location (Study period)	Case Definitions	Descriptions of Case Definitions	Surveillance Method	Sample Size	Main findings and authors conclusions (in relevance to COVID-19 surveillance)
Pannu, 2021[32]	Chandigarh, India (March 2020 to August 2020)	modified **SARI	febrile respiratory symptoms, OR radiographic evidence of pneumonia, OR acute respiratory distress syndrome of ≤14 days duration, AND a need for hospitalisation, in the absence of an alternative aetiology that fully explains the illness	COVID-19 SARI and non-COVID- 19 SARI cases presenting to the adult emergency department of a hospital were compared	212	• 95 (44.8%) patients had confirmed SARS-CoV-2 infection • Mortality was high in both groups (COVID and non-COVID SARI) • COVID- 19 required prolonged hospitalisation • Including chest radiography into the WHO SARI definition might improve a COVID-19 surveillance model in a hospital setting.
Public Health England, 2020[33]	United Kingdom (2018 to 2020)	***ILI	ECDC	Data on ILI collected from Public Health England real-time surveillance systems, monitoring multiple ILI indicators - i.e., NHS 111 Cold/flu calls and GP consultations for ILI	Not available	• Low levels of ILI activity across UK in 2019 and 2020 - predominantly influenza A(H3N2). Increased numbers of all-cause mortality for all ages were observed in influenza seasons 2019-2020 (7990, CI: 7489 to 8502) as compared to 2018-2019 (3966, CI: 3597 to 4347). GP sentinel swabbing and GP ILI consultations rates dropped during these years due to the pandemic - resulting in a decrease in surveilled cases • Decrease in detected influenza cases may be due to reduced surveilled cases as patients had less visitations to GP offices for consultations. The excess mortality was in line with increases in deaths related to the COVID-19 pandemic.

***ARI:** Acute respiratory infection
****SARI:** Severe acute respiratory infection
*****ILI:** Influenza-like-illness
******RSV:** Respiratory syncytial virus
The footnotes to the descriptions of case definitions are provided in appendix 3.2

Limitations

A few limitations of this review include no formal quality assessment of included studies and low sample sizes (<1000) of two included studies. It may also be important to note that 87.5% of the studies were conducted in Europe (Italy (3), Belgium (1), United Kingdom (1), Spain (1) and Germany (1)). With new variants being reported in different parts of the world, it is likely that clinical symptoms may be slightly different depending on local circulating variants that might impact the performance of these case definitions in each setting.

Conclusions

ILI and SARI case definitions have mainly been used for COVID-19 surveillance. The findings of our review indicate that ILI and SARI syndromic surveillance and ILI laboratory-based surveillance were effective in detecting COVID-19 cases. However, the performance of these surveillance systems was not formally evaluated in any of the studies and therefore, studies evaluating specificity and sensitivity are warranted.

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	Asymptomatic		Central nervous system		Musculoskeletal
	General		ENT		Dermatological
	Cardiorespiratory		Gastro-intestinal		

APPENDIX

Appendix Table 2.1: Summary of clinical features reported in reviews ordered by system

Lead author, year	Last date of search	Country	Age group	Severity	Data availability for pooled estimate of symptom prevalence																								
					Asymptomatic	Fever	Chills/shivering	Cough	Expectoration	Shortness of breath	Chest pain	Chest tightness	Haemoptysis	Hypoxemia	Palpitation	Dizziness	Headache	Impaired consciousness	Seizures	Loss of taste/smell	Rhinorrhoea	Nasal congestion	Sore throat	Abdominal pain	Loss of appetite	Diarrhoea	Nausea/vomiting	Myalgia	Fatigue	Rash
***Akin H, 2020[5]**	19-09-2020	Global	All ages	All		✓																	✓	✓	✓	✓			
Aziz M, 2021[6]	06-08-2020	Global	All ages	All																✓										
Aziz M, 2020[7]	31-05-2020	Global	All ages	All																					✓	✓			
***Badal S, 2020[8]**	16-06-2020	Global	Children	All	✓	✓		✓		✓							✓				✓	✓	✓					✓	✓	
***Bennett S, 2020[9]**	26-04-2020	Global	Adults	All	✓	✓	✓	✓	✓	✓			✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
***Bhuiyan MU, 2021[10]**	04-06-2020	Global	Children	All	✓	✓																								
***Christophers B, 2020[11]**	15-05-2020	Global	Children	All		✓		✓									✓		✓				✓			✓	✓	✓		
Chua TH, 2020[12]	11-05-2020	Global	Adults	All																✓										
Gaythorpe K, 2021[13]	04-07-2020	Global	Children	All	✓																									
***Ghimire S,**	05-2020	Global	All ages	All																					✓	✓			

Lead author, year	Last date of search	Country	Age group	Severity	Data availability for pooled estimate of symptom prevalence																								
					Asymptomatic	Fever	Chills/shivering	Cough	Expectoration	Shortness of breath	Chest pain	Chest tightness	Haemoptysis	Hypoxemia	Palpitation	Dizziness	Headache	Impaired consciousness	Seizures	Loss of taste/smell	Rhinorrhoea	Nasal congestion	Sore throat	Abdominal pain	Loss of appetite	Diarrhoea	Nausea/vomiting	Myalgia	Fatigue	Rash
2021[14]																													
Hasani H, 2020[15]	25-03-2020	China	All ages	All		✓		✓	✓	✓			✓				✓					✓			✓	✓		✓	
***Hashan MR 2021[16]**	28-09-2020	Global	Adults	All	✓	✓		✓		✓				✓		✓	✓			✓	✓		✓		✓	✓	✓	✓	✓	✓
Kim H, 2021[17]	08-06-2020	Global	All ages	All		✓		✓	✓	✓		✓				✓	✓				✓		✓	✓	✓	✓	✓	✓	
Mutiawati E 2021[18]	02-09-2020			All													✓												
Mutiawati E 2021[19]	10-11-2020	Global	All ages	All																✓									
Rogers JP 2021[20]	18-07-2020	Global	All ages	All													✓			✓							✓	✓	
Saniasiaya J 2020[21]	23-07-2020	Global	All ages	All																✓									
Syangtan G 2021[22]	30-04-2020	Global	All ages	All	✓																								
***Wang J, 2021[23]**	20-10-2020	Global	Children	All	✓	✓																							
***Xie J, 2021[24]**	18-03-2020	Asia/ Pacific	Adults	All		✓	✓	✓		✓	✓		✓			✓	✓											✓	
Yang J, 2020[25]	25-02-2020	China	All ages	All		✓		✓		✓										✓	✓	✓	✓	✓	✓	✓		✓	

*Excluded features that were non-specific or multiple features grouped together (the number of reviews where these exclusions apply in brackets): gastrointestinal symptoms (4), respiratory symptoms including upper and lower respiratory symptoms (3), nasal symptoms (2), chest distress (1), weakness (1), myalgia or arthritis as a combined category (1), others as a combined category of several symptoms or signs (2).

Appendix Table 2.2: Detailed findings from individual reviews on clinical features

Authors	Age group	Clinical features	No. of study	No. of patients	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI
Akin H, 2020[5]	all	Fever	45	74543	73	70	76
Akin H, 2020[5]	all	Abdominal pain	38	34713	6	4	7
Akin H, 2020[5]	all	Loss of appetite	37	22743	18	10	27
Akin H, 2020[5]	all	Diarrhoea	44	62892	15	12	19
Akin H, 2020[5]	all	Nausea/vomiting	44	46390	10	8	12
Aziz M, 2021[6]	all	Loss of taste/smell	51	11074	52	42.5	61.6
Aziz M, 2020[7]	all	Diarrhoea	83	26912	13	10.8	15.5
Aziz M, 2020[7]	all	Nausea/vomiting	83	26912	9.5	7.9	11.4
Badal S, 2020[8]	children	Asymptomatic	20	222	13	11	14
Badal S, 2020[8]	children	Fever	19	592	55	52	58
Badal S, 2020[8]	children	Cough	17	467	45	42	49
Badal S, 2020[8]	children	Shortness of breath	11	169	19	16	22
Badal S, 2020[8]	children	Headache	5	117	67	60	74
Badal S, 2020[8]	children	Rhinorrhoea	9	38	6	4	8
Badal S, 2020[8]	children	Nasal congestion	8	69	20	16	25
Badal S, 2020[8]	children	Sore throat	11	18	3	2	4
Badal S, 2020[8]	children	Muscle pain	7	194	35	32	40
Badal S, 2020[8]	children	Fatigue	6	53	9	7	11
Bennett S, 2020[9]	adults	Asymptomatic	3	1231	2.8		
Bennett S, 2020[9]	adults	Fever	26	7789	81.2		
Bennett S, 2020[9]	adults	Chills/Shivering	5	1844	19.7		
Bennett S, 2020[9]	adults	Cough	25	7546	62.9		
Bennett S, 2020[9]	adults	Expectoration	12	3460	24.2		
Bennett S, 2020[9]	adults	Shortness of breath	22	7030	26.9		
Bennett S, 2020[9]	adults	Haemoptysis	5	2147	1.7		
Bennett S, 2020[9]	adults	Dizziness	6	2031	8.1		
Bennett S, 2020[9]	adults	Headache	18	6047	11.4		
Bennett S, 2020[9]	adults	Impaired consciousness	5	3026	12.4		
Bennett S, 2020[9]	adults	Loss of taste/smell	2	342	25.4		
Bennett S, 2020[9]	adults	Rhinorrhoea	5	1831	12.1		
Bennett S, 2020[9]	adults	Nasal congestion	6	3334	10.8		
Bennett S, 2020[9]	adults	Sore throat	17	5767	13.1		
Bennett S, 2020[9]	adults	Abdominal pain	8	3205	3		
Bennett S, 2020[9]	adults	Loss of appetite	6	1124	33.7		
Bennett S, 2020[9]	adults	Diarrhoea	22	6572	13.1		
Bennett S, 2020[9]	adults	Nausea/vomiting	17	5703	6.5		
Bennett S, 2020[9]	adults	Muscle pain	14	5615	14.4		

Authors	Age group	Clinical features	No. of study	No. of patients	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI
Bennett S, 2020[9]	adults	Fatigue	12	4280	38		
Bennett S, 2020[9]	adults	Palpitation	2	272	5.5		
Bhuiyan MU, 2021[10]	children	Asymptomatic	9	42	43	15	73
Bhuiyan MU, 2021[10]	children	Fever	18	43	76	61	89
Christophers B, 2020[11]	children	Fever	22	75	61.5		
Christophers B, 2020[11]	children	Cough	22	50	41		
Christophers B, 2020[11]	children	Headache	22	2	1.6		
Christophers B, 2020[11]	children	Sore throat	22	18	14.8		
Christophers B, 2020[11]	children	Diarrhoea	22	19	15.4		
Christophers B, 2020[11]	children	Nausea/vomiting	22	6	4.9		
Christophers B, 2020[11]	children	Muscle pain	22	5	4.1		
Christophers B, 2020[11]	children	Seizure	22	2	1.6		
Chua TH, 2020[12]	adults	Loss of taste/smell	3	703	59.9		
Gaythorpe K, 2021[13]	children	Asymptomatic	14		21.1	14	28.1
Ghimire S, 2021[14]	all	Diarrhoea	37	8352	11.52	8.97	14.68
Ghimire S, 2021[14]	all	Nausea/vomiting	26	7196	7.53	5.27	10.65
Hasani H, 2020[15]	all	Fever	14		84.3	78.6	88.7
Hasani H, 2020[15]	all	Cough	14		60.1	53.5	66.4
Hasani H, 2020[15]	all	Expectoration	5		23.9	16.4	33.4
Hasani H, 2020[15]	all	Shortness of breath	8		17.1	9.1	29.8
Hasani H, 2020[15]	all	Haemoptysis	5		2.3	0.9	5.7
Hasani H, 2020[15]	all	Headache	12		9.1	7	11.8
Hasani H, 2020[15]	all	Sore throat	5		13	8.5	19.3
Hasani H, 2020[15]	all	Diarrhoea	11		6.4	4.3	9.5
Hasani H, 2020[15]	all	Nausea/vomiting	2		10.9	3.8	27.5
Hasani H, 2020[15]	all	Fatigue	11		39.4	29.1	50.8
Hashan MR, 2021[16]	adults	Asymptomatic	13	985	31	28	34
Hashan MR, 2021[16]	adults	Fever	13	1872	49	47	52
Hashan MR, 2021[16]	adults	Cough	14	1876	45	43	47
Hashan MR, 2021[16]	adults	Shortness of breath	10	1497	29	27	32
Hashan MR, 2021[16]	adults	Dizziness	2	89	5	2	12
Hashan MR, 2021[16]	adults	Headache	7	1116	4	3	5
Hashan MR, 2021[16]	adults	Loss of taste/smell	2	313	1	0	1

Authors	Age group	Clinical features	No. of study	No. of patients	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI
Hashan MR, 2021[16]	adults	Rhinorrhoea	5	1331	5	4	6
Hashan MR, 2021[16]	adults	Sore throat	6	1128	5	4	7
Hashan MR, 2021[16]	adults	Loss of appetite	9	1712	14	13	16
Hashan MR, 2021[16]	adults	Diarrhoea	7	647	12	10	15
Hashan MR, 2021[16]	adults	Nausea/vomiting	6	528	6	4	8
Hashan MR, 2021[16]	adults	Muscle pain	5	256	3	1	6
Hashan MR, 2021[16]	adults	Fatigue	5	1162	7	6	9
Hashan MR, 2021[16]	adults	Hypoxia	5	373	33	29	38
Hashan MR, 2021[16]	adults	Rash	1	103	1	0	7
Kim H, 2021[17]	all	Fever	32		79	70	86
Kim H, 2021[17]	all	Cough	31		65	60	70
Kim H, 2021[17]	all	Expectoration	16		27	20	35
Kim H, 2021[17]	all	Shortness of breath	28		43	34	52
Kim H, 2021[17]	all	Dizziness	5		14	4	28
Kim H, 2021[17]	all	Headache	19		12	8	16
Kim H, 2021[17]	all	Rhinorrhoea	5		8	4	12
Kim H, 2021[17]	all	Sore throat	15		9	6	12
Kim H, 2021[17]	all	Abdominal pain	5		4	1	9
Kim H, 2021[17]	all	Loss of appetite	8		58	43	72
Kim H, 2021[17]	all	Diarrhoea	25		14	10	19
Kim H, 2021[17]	all	Nausea/vomiting	12		12	7	17
Kim H, 2021[17]	all	Nausea/vomiting	7		8	2	18
Kim H, 2021[17]	all	Muscle pain	22		22	17	27
Kim H, 2021[17]	all	Fatigue	17		44	32	55
Kim H, 2021[17]	all	Chest tightness	10		21	11	33
Mutiawati E, 2021[18]	all	Loss of taste/smell	107	32142	38.2	36.5	47.2
Mutiawati E, 2021[19]	all	Headache	78	104751	25.26		
Rogers JP, 2021[20]	all	Headache	34		37.5	29.3	46.5
Rogers JP, 2021[20]	all	Loss of taste/smell	36		42.4	34.4	50.9
Rogers JP, 2021[20]	all	Muscle pain	30		38.6	29.6	48.5
Rogers JP, 2021[20]	all	Fatigue	24		43.3	33.2	54.1
Saniasiaya J, 2020[21]	all	Loss of taste/smell	81	27354	48.4	41.67	55.12
Syangtan G, 2021[22]	all	Asymptomatic	16	2788	48.2	30	60
Wang J, 2021[23]	children	Asymptomatic	20	7664	24.8	18.6	31.5
Wang J, 2021[24]	children	Fever	29	6282	51.7	43.8	59.6

Authors	Age group	Clinical features	No. of study	No. of patients	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI
Xie J, 2021[25]	adults	Fever	65	10881	78.4	74.5	82.3
Xie J, 2021[25]	adults	Chills/Shivering	14	3841	13.7	8.1	19.2
Xie J, 2021[25]	adults	Chest pain	17	3197	3.9	2.4	5.4
Xie J, 2021[25]	adults	Cough	62	10571	58.5	51.4	65.6
Xie J, 2021[25]	adults	Expectoration	35	6964	22.7	18.2	27.2
Xie J, 2021[25]	adults	Shortness of breath	19	5964	18.5	12.9	24.2
Xie J, 2021[25]	adults	Haemoptysis	6	2039	1.7	0.7	2.8
Xie J, 2021[25]	adults	Dizziness	10	1831	4.2	2.5	5.9
Xie J, 2021[25]	adults	Headache	35	7379	9.3	7.6	11
Xie J, 2021[25]	adults	Fatigue	45	8938	26.4	21.4	31.4
Yang J, 2020[26]	all	Fever	7	1576	91.3	86	97
Yang J, 2020[26]	all	Cough	7	1576	67.7	59	76
Yang J, 2020[26]	all	Shortness of breath	7	1576	30.4	21	40
Yang J, 2020[26]	all	Rhinorrhoea	16	3051	5.5	3.5	7.5
Yang J, 2020[26]	all	Nasal congestion	9	2712	5.1	2.4	7.8
Yang J, 2020[26]	all	Sore throat	33	5808	9.2	7.4	11
Yang J, 2020[26]	all	Abdominal pain	12	1586	3.3	2.2	4.6
Yang J, 2020[26]	all	Loss of appetite	16	2623	12.9	8.7	17
Yang J, 2020[26]	all	Diarrhoea	46	8278	6.8	5.4	8.2
Yang J, 2020[26]	all	Nausea/vomiting	9	1004	6.6	3.8	9.4
Yang J, 2020[26]	all	Nausea/vomiting	12	1591	3.3	2.4	4.2
Yang J, 2020[26]	all	Fatigue	7	1576	51	34	68

Appendix 2.3: Figures for sensitivity analysis looking at latest reviews for all ages, children, and adults

Figure S1. Prevalence of each symptom in all ages, extracted from the latest review only

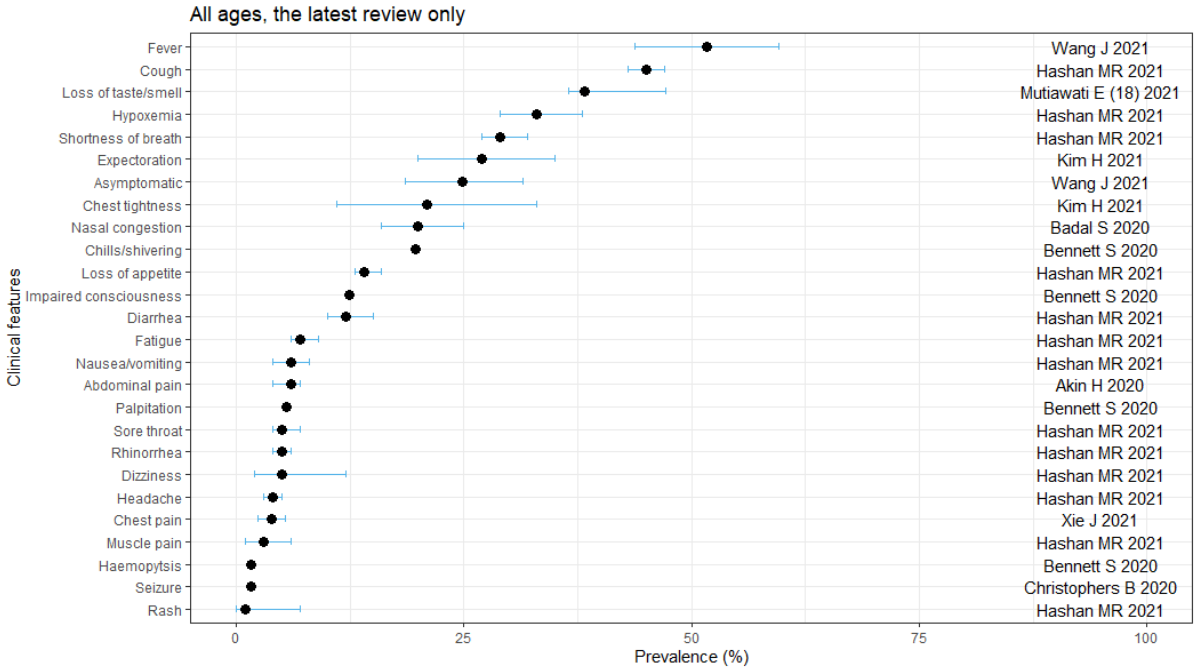


Figure S2. Prevalence of each symptom in children, extracted from the latest review only

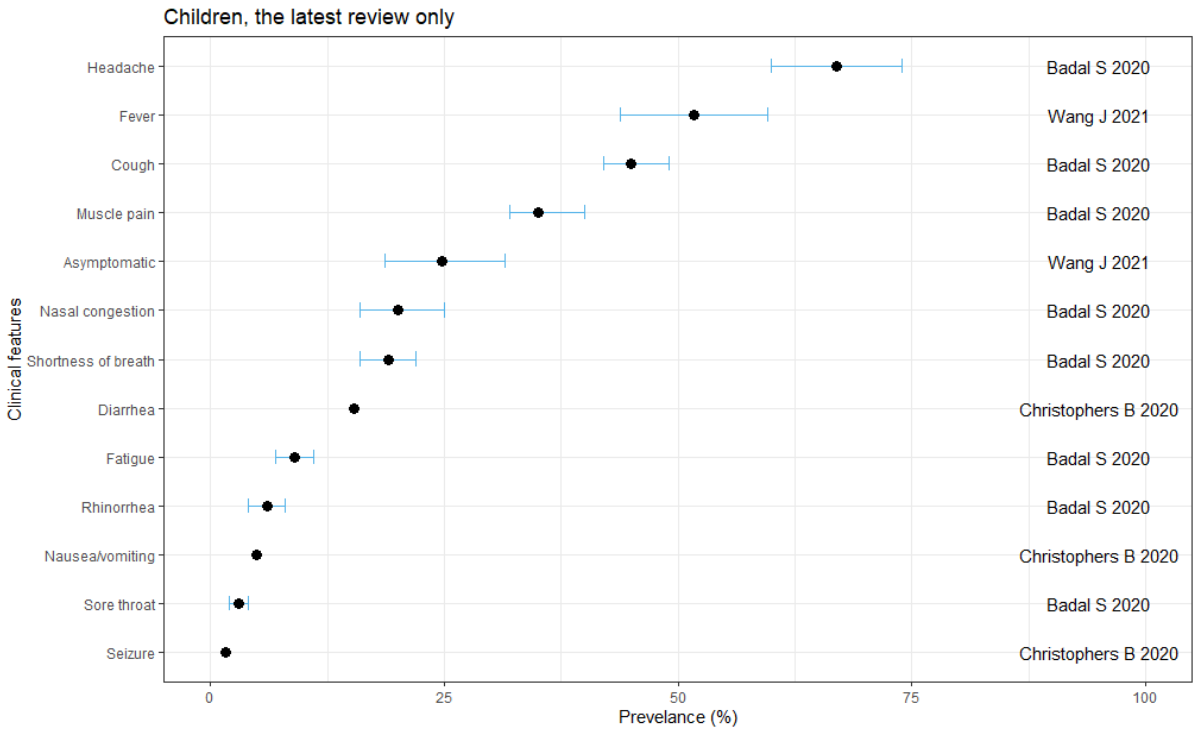


Figure S3. Prevalence of each symptom in adults, extracted from the latest review only

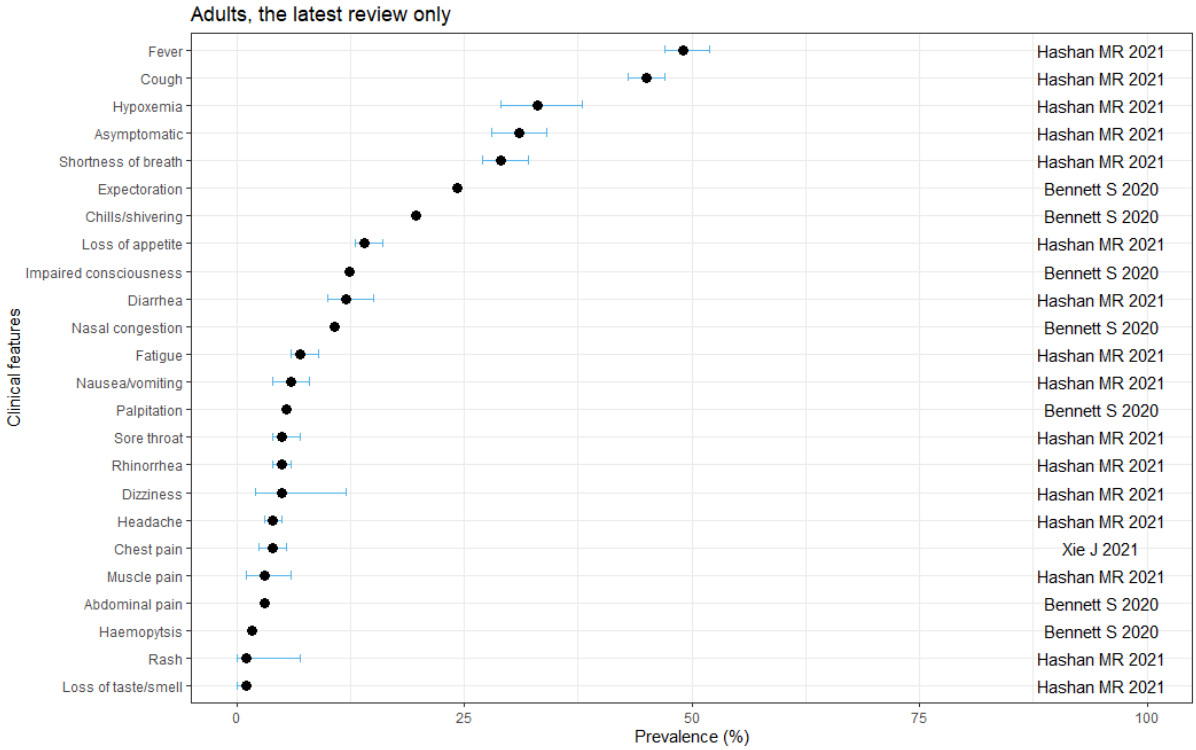


Figure S4. Prevalence of each symptom in all ages, extracted from reviews having at least five clinical features only (n= 9)

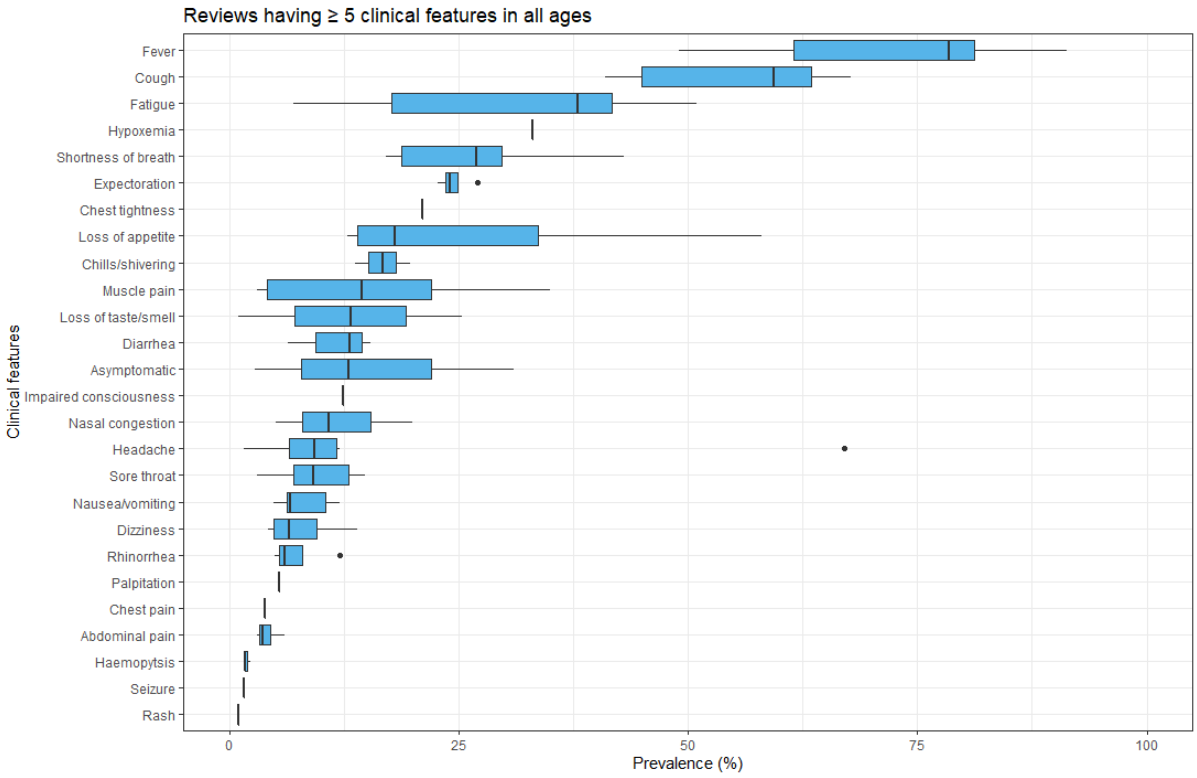


Figure S5. Prevalence of each symptom in children, extracted from reviews having at least five clinical features only (n= 2)

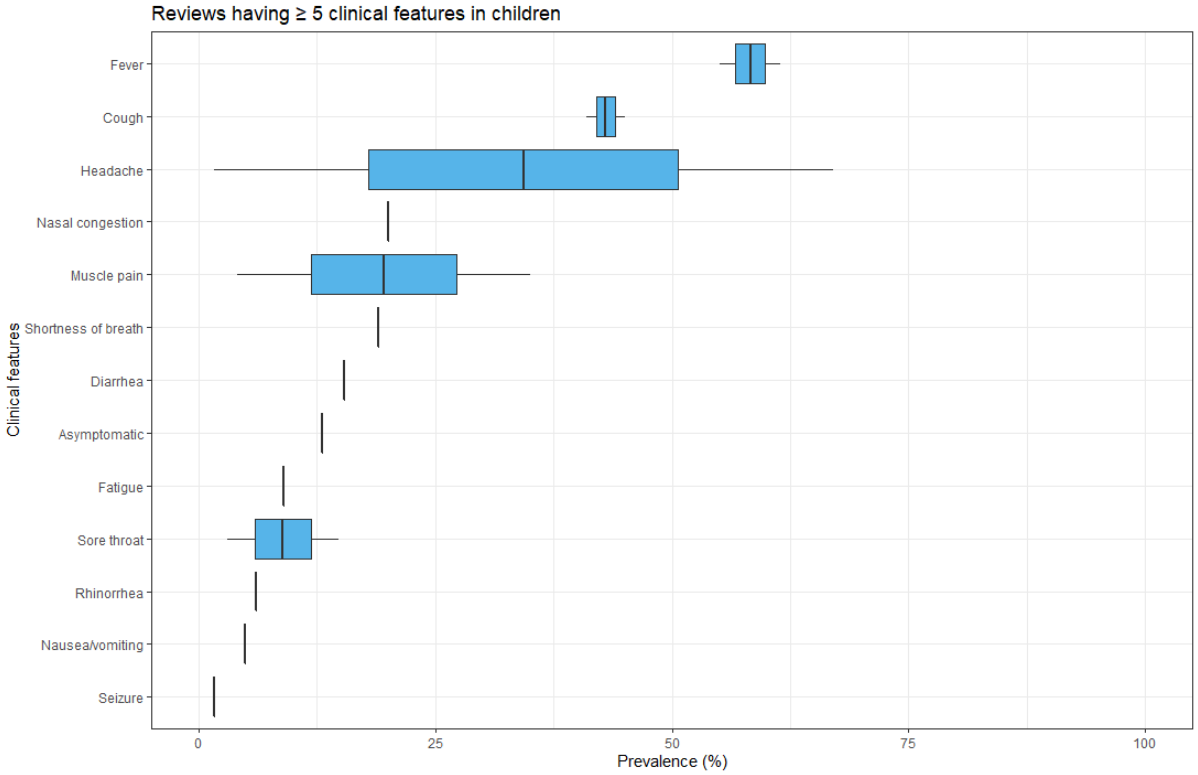
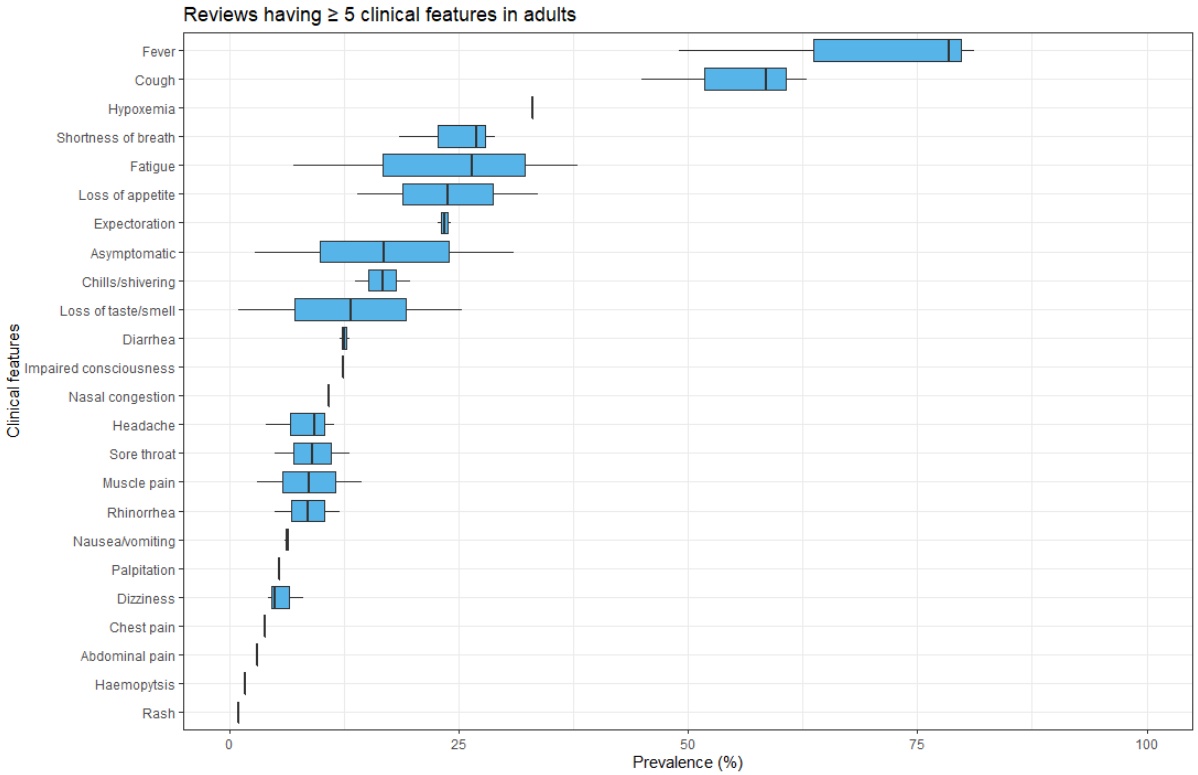


Figure S6. Prevalence of each symptom in adults, extracted from reviews having at least five clinical features only (n= 3)



Appendix 3.1: Search strategy of the review on the performance of COVID-19 surveillance based on existing flu surveillance

Strategy A

gisrs OR “global influenza” OR sentinel OR ((mh: “mass screening” OR ti:surveill* OR ab:surveill* OR mh: “population surveillance” OR network* OR monitor* OR “early warning”) AND (h1n1 OR sari OR mh: “respiratory tract infection” OR mh: “respiratory tract disease” OR mh: “respiratory distress syndrome” OR influenza OR influensa OR flu OR grippe OR ili OR “acute respiratory infection” OR “acute respiratory infections”))

Strategy B

(sari OR gisrs OR “global influenza” OR sentinel OR mh: “mass screening” OR ti:surveill* OR ab:surveill* OR mh: “surveillance” OR network* OR monitor* OR “early warning” OR mh: “respiratory tract infection” OR mh: “respiratory tract disease” OR mh: “respiratory distress syndrome” OR influenza OR influensa OR flu OR grippe OR ili OR “acute respiratory infection” OR “acute respiratory infections”) AND (sensitiv* OR specific*)

Appendix 3.2: Footnotes to the 'descriptions of case definitions' in table 3.1

[1]***ECDC – ILI:*** Sudden onset of symptoms **AND** at least 1 of the following four systemic symptoms:

- Fever
- Malaise
- Headache
- Myalgia

AND

at least one of the three following respiratory symptoms:

- Cough
- Sore throat
- Shortness of breath

ICD-10 Codes

[2]***J00 – J06: Acute Respiratory Infections***

J00: Acute nasopharyngitis (Common cold) - Catarrhal disorder of the upper respiratory tract characterised by:

- Runny nose
- Nasal congestion
- Sneezing
- Chills
- Headaches
- Coughing
- Facial pain
- Sore throat

J01: Acute sinusitis – including the following characteristics:

- acute abscess of sinus
- acute empyema of sinus
- acute infection of sinus
- acute inflammation of sinus
- acute suppuration of sinus

J02: Acute pharyngitis – characterised by acute sore throat

J03: Acute inflammation of tonsils **AND** other symptoms, including:

- Fever
- Enlargement of tonsils
- Difficulty swallowing
- Enlargement of regional lymph nodes

J04: Acute laryngitis and tracheitis

J05: Acute obstructive laryngitis and epiglottitis

J06: Acute upper respiratory infections of multiple and unspecified sites, symptoms including:

- Congestion
- Coughing
- Sneezing
- Sore throat

[3]***J09 – J18: Influenza and pneumonia***

J09: Influenza due to certain identified influenza viruses, characterised by:

- Laryngitis
- Pharyngitis
- Respiratory manifestations (Necrotising enterocolitis (NEC))
- Digestive/ gastrointestinal manifestations
- Enteritis/ gastroenteritis
- Encephalopathy
- Myocarditis
- Otitis media

J10: Influenza due to other identified influenza virus

J11: Influenza due to unidentified influenza virus

J12: Viral pneumonia, not elsewhere classified

J13: Pneumonia due to Streptococcus pneumoniae, described as a febrile disease

J14: Pneumonia due to Hemophilus influenzae

J15: Bacterial pneumonia, not elsewhere classified, including bronchopneumonia

J16: Pneumonia due to other infectious organisms, not elsewhere classified

J17: Pneumonia in diseases classified elsewhere, including the following underlying diseases:

- Q-fever
- Rheumatic fever
- Schistosomiasis

J18: Pneumonia, unspecified organism

[4]***J20 – J22: Other acute lower respiratory infections***

J20: Acute bronchitis - inflammation of the bronchial tubes, involving the following symptoms:

- Cough
- Shortness of breath
- Wheezing
- Tightness of chest

J21: Acute bronchiolitis

J22: Unspecified acute lower respiratory infection

[5]**J44.0:** Chronic obstructive pulmonary disease with (acute) lower respiratory infection

[6]**B34.9:** Unspecified viral infection – A general term, which includes:

- Any disease caused by a virus
- The presence of viruses in the blood

[7]**B97.4:** Respiratory syncytial virus as the cause of diseases classified elsewhere

[8]**U07.1:** COVID-19, virus identified - Lab confirmed COVID-19, regardless of severity of the disease

[9]**U07.2:** COVID-19, virus not identified - Clinical or epidemiological diagnosis of COVID-19, without lab confirmation.