Spatial and temporal dynamics of SARS-CoV-2 in COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

Background: The spatial and temporal dynamics of SARS-CoV-2 have been described in case series and retrospective studies. In this study, we provide a coherent overview of the duration of viral detection and viral RNA load in COVID-19 patients, stratified by specimen type, clinical severity, and age.

Method: We systematically searched PubMed/MEDLINE and Cochrane review database for studies published between 1.11.2019 and 23.04.2020. We pooled the data of selected studies (22/7226 (650 patients) for meta-analysis) to estimate duration of viral detection and visualized viral load over time.

Findings: Our analysis showed consistent viral detection from specimen from the upper respiratory tract (URT), the lower respiratory tract (LRT), and faeces, irrespective of the clinical severity of COVID-19. Our analysis suggests that SARS-CoV-2 persists for a longer duration in the LRT compared to the URT in adult patients (5–7 days in mild; 5–9 days in moderate-severe patients). The differences in the duration of viral detection between mild and moderate-severe patients is limited in the LRT, but an indication of longer duration of viral detection for moderate-severe patients was observed in feces (15 days in mild vs. 21 days in moderate-severe patients) and the URT (12 days in mild vs. 16 days in moderate-severe patients). Further, viral load was demonstrated to peak in earlier stages of infection in the URT compared to LRT.

Interpretation: This review may aid mathematical modelling and help in defining appropriate endpoints for clinical trials with antivirals in COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19) has caused many deaths and severe suffering worldwide prompting a surge in research and drug development activities. These efforts are revealing clinical and molecular characteristics of SARS-CoV-2 and the infection it causes, but its viral dynamics and spatial shedding patterns in humans remain poorly understood [1]. A variety of case series and retrospective studies, reporting viral dynamics of SARS-CoV-2 on a patient or patient population level, have been published and illuminate the spatial patterns of SARS-CoV-2’s shedding in different stages of the infection[1]. However, these studies are heterogeneous with regards to patient populations and the specific viral RNA load testing. To provide an overview of our current knowledge of the shedding patterns of SARS-CoV-2, we conducted a review of the temporal and spatial viral dynamics across clinical severities of COVID-19. Firstly, this knowledge can help improve mathematical models of SARS-CoV-2’s replication, as the numerical model can be trained with more real-world data. Secondly, this knowledge can inform the definition of relevant endpoints in clinical trials assessing pharmacological treatments aimed at reducing viral RNA load in patients positive for SARS-CoV-2.

The objective of this paper is to provide a systematic review of the spatial and temporal viral dynamics of SARS-CoV-2 in COVID-19 patients, stratified after clinical severity, location of viral sampling and age, based on individual patient data. The data of the systematic review is then aggregated to report a weighted mean of duration of viral detection, per sampling location for adults and children with mild and moderate-severe symptoms.

2. Materials and methods

This systematic review and subsequent meta-analysis have been conducted according to the PRISMA guidelines [2]. A PRISMA checklist is displayed in Table S1.
2.1. Systematic review

2.1.1. Data sources

We searched the databases MEDLINE/PUBMED and Cochrane Review with the following search terms: “SARS-CoV-2 [MESH]” OR “COVID 19 [MESH]” alone, or in combination with “virology” OR “viral” OR “Epidemio” AND “clinical”. Studies from November 2019 until 23rd of April 2020 are included in this review.

2.1.2. Eligibility criteria

The inclusion criteria with the corresponding rational is summarized in Table 1. Studies which demonstrated viral data as patient fractions (e.g. as Kaplan Meyer Plots), missed crucial information needed for detailed stratification (e.g. age, clinical severity, individual viral RNA load/dynamic data), contained only asymptomatic patients or could be classified as interventional study were excluded. Given the rather simple study setup (one primary outcome investigated with predefined outcome measure criteria) and precise and narrow eligibility criteria, the study evaluation was performed by only one reviewer. In the rare case of uncertainties, these were discussed and resolved by consensus with all authors of this manuscript or with the support of internal medical specialists.

2.1.3. Study selection

Following screening of titles and removing of duplicates, relevant abstracts were selected for screening. Out of the abstracts, studies were selected to be scanned as full text to assess eligibility. Finally, studies were selected to be included in the systematic review.

2.1.4. Data extraction

Data were extracted from the full text/supplemental material or if only available in graphs digitalized using GetData Graph Digitizer © version 2.26.0.20. We used a pre-defined and internally developed extraction protocol to capture identical information across studies (incl. author, title, country, design, sample size, thresholds and genes of RT-PCR, frequency of sampling, patient age (median), COVID-19 severity and classification reference, major clinical characteristics, treatment, location of viral sampling, duration of viral detection, viral RNA load).

2.1.5. Data processing and summary measures

To determine the duration of viral detection from symptom onset, we counted the days from initiation of symptoms (Day 0) to the last positive test (final day was set as Day -1 of first negative test of two consecutive tests for daily sampling). However, in some studies the sampling frequency was not daily, meaning that the last positive test does not equal Day -1 of first negative test. Therefore, we also reported the duration of viral detection until the last positive swab, to not introduce any predictions into the summary measures. In the case that the day of the positive test was not reported for a patient, we excluded this patient in the overall summary measure, as the duration of viral detection becomes predictive. Also, in case a positive test was not reported, we could not be sure that this patient was tested at all positive for the virus at the specific sampling location. Furthermore, for patients that did not clear the virus within the time frame of sampling, we used the day of the last positive test as final day to not introduce bias into the data by excluding these and leaving out patients that needed longer to clear the virus than the average. Finally, we also recorded the duration of viral detection in case recurrence of positivity was observed, meaning a positive test was detected after two negative ones have been obtained. To measure the duration in regard to the “recurrence” endpoint, the final day was also set as Day -1 of the first negative test of two consecutive negative tests.

In case clinical severity was not categorized into mild, moderate or severe by the authors of the publication, we conducted this categorization with the symptoms reported, based on definitions described by Wu et al. [3]. Asymptomatic patients were excluded.

Duration of viral detection is demonstrated as mean (days after symptom or admission onset) with its corresponding standard deviation and viral RNA load was visualized as viral copies/mL [log10] over time (days after symptom onset) stratified after clinical severity, mild or moderate/severe, and location of swab (upper respiratory tract (URT) specimen, lower respiratory tract (LRT) specimen or faeces). Oro-/nasopharyngeal, throat and nasal swabs were combined to “URT”, sputum and tracheal aspirate to “LRT”, anal swabs and stool to “faeces”, and plasma and serum to “Blood”. Data which did not use copies/mL as unit for quantifying viral RNA load were excluded. R Studio ©, Version 1.2.1335 was used for visualization. Raw data can be found in Supplementary Table S2.

2.1.6. Statistical analysis of viral RNA load comparison

Statistical analysis comparing the average load per sampling location across each study was performed using unpaired t test, not assuming consistent SD and using a two stage setup false discovery rate approach of Benjamini, Krieger and Yekutieli, setting the desired FDR to 1% [4]. Statistical analysis was conducted in GraphPad Prism 8.1.2.

2.2. Meta-analysis

2.2.1. Study selection

Out of the studies that were included in the systematic review, we chose studies to be included in the meta-analysis which measured duration of positive detection of SARS-CoV-2 in days after symptom onset, but not after hospitalization ensuring that an identical Day 0 is set across. Patients equal to 18 years or older were classified as adults (if only median was recorded, the median age was considered for categorization). Single case series were excluded. In total, 22 studies were included in the aggregation of data [5–26].
### 2.2.2. Risk of bias assessment

The risk was assessed based on pre-defined criteria and included both the assessment on a study and outcome measure level. The results of the assessment of risk of bias for each study of the meta-analysis is summarized in Table S3. The possibility of publication bias was assessed using funnel-plot asymmetry as suggested by Egger et al. which was analysed in RStudio with the metafor package [27,28].

### 2.2.3. Data processing

Mild disease severity was kept as mild and moderate and severe disease severity were merged to moderate-severe in the meta-analysis. Oro-/nasopharyngeal, throat and nasal swabs were combined to “URT”, sputum and tracheal aspirate to “LRT”, anal swabs and stool to “faeces”, and plasma and serum to “Blood”.

### 2.2.4. Data synthesis and statistical analysis

Aggregation of study data of duration of viral detection was conducted in ReviewManager 5.3. Standard error was computed according to \( \text{STDEV}/(\text{SQRT}(N)) \). We used generic inverse variance as a data type (mean and SE), and random effect as analysis model. Effect measures (pooled estimates) were shown as mean or differences in mean with 95% confidence interval (CI). Mean differences in each study was computed based on a per patient calculation. Heterogeneity was measured by $I^2$. Forest plots are provided for selected data groupings.

### 3. Results

#### 3.1. Study selection

The overall study selection process is displayed in the flow-diagram in Fig. 1. Briefly, we screened a total of 7226 titles and selected 553 for abstract screening. Out of the 553 abstracts, we selected 143 studies to be scanned as full text to investigate whether viral data is generally reported. Out of these studies, 80 studies were chosen for in-depth reading to assess eligibility. Finally, 37 studies were included in the systematic review. Reasons for exclusion were: individual patient data was missing and/or only median of duration of viral detection was demonstrated, clinical severity or age was not reported or only baseline viral data were shown.

#### 3.2. Overview of studies describing duration of viral detection in COVID-19 patients

The data summary of the selected studies, describing duration of viral detection as days after symptom onset (as mean and SD) is displayed in Table 2 and days after hospitalization in Table 3. More details of each study, including clinical characteristics can be found in Table S4 in the supplementary material.

The SARS-CoV-2 virus is detected in both in the lower and upper respiratory tract, and faeces, irrespective of the severity of the disease.
| No. | Author | Design | Threshold Gene | Age* | Clinical severity | Reported Treatment | Size | Sampling Location | 2 consecutive negatives Last positive | 2 consecutive negatives Last positive |
|-----|--------|--------|----------------|------|------------------|-------------------|------|-------------------|-------------------------------------|-------------------------------------|
|     |        |        |                |      |                  |                    |      |                   | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 1   | Cai J. [5] | Case series | Ct \( \geq 35 \) ORF1ab,N | 6-5 | Mild | NS | 10 | Nasopharyngeal | 12.0 | 4.8 | 12.0 | 6.1 | 20.0 | 6.5 | 20.0 | 6.1 |
| 2   | Caly [33] | Case series | NS | 58 | 0 | Moderate | None | 1 | Nasopharyngeal | 11.0 | NA | 8.0 | NA | 11.0 | NA | 8.0 | NA |
| 3   | Chang [6] | Case series | NS | 35 | 5 | Mild | aIFN, L/R or other ANs | 16 | Stool | 8.6 | 3.8 | 12.0 | 6.5 | 20.0 | 6.1 |
| 4   | Chen [17] | RS | ORF1ab,N | 39 | 0 | Moderate | NS | 16 | Sputum | 10.9 | 4.9 | 8.3 | 3.9 | 12.6 | 6.7 | 11.0 | 6.5 |
| 5   | Chen [31] | Case series | NS | 46 | 0 | Moderate | NS | 1 | Nasopharyngeal | 11.0 | NA | 8.0 | NA | 19.0 | NA | 17.0 | NA |
| 6   | Cheng [34] | Case series | TCDC | 55 | 0 | Moderate | NS | 1 | Nasopharyngeal | 11.0 | NA | 8.0 | NA | 19.0 | NA | 17.0 | NA |
| 7   | Colavita [29] | Case series | NS | 58 | 0 | Mild | NS | 1 | Nasopharyngeal | 10.0 | NA | 8.0 | NA | 19.0 | NA | 17.0 | NA |
| 8   | Grace Lui [20] | Prospective | Cohort Study | > 694 copies/mL | 58 | 0 | Moderate | NS | 1 | Nasopharyngeal | 10.0 | NA | 8.0 | NA | 19.0 | NA | 17.0 | NA |
| 9   | Han [21] | Case series | [35] | 44 | 0 | Mild | NS | 22 | Sputum | 15.4 | 5.7 | 13.0 | 4.5 | 16.8 | 8.3 | 14.6 | 9.2 |
| 10  | Holshue [36] | Case series | CDC | 35 | 0 | Moderate | NS | 1 | Nasopharyngeal | 11.0 | NA | 8.0 | NA | 19.0 | NA | 17.0 | NA |
| 11  | Hu [15] | Case series | ORF1ab, N | 28 | 0 | Mild | NS | 11 | Nasopharyngeal | 11.7 | 2.3 | 11.0 | 2.6 | 18.3 | 8.4 | 18.0 | 8.4 |
| 12  | Hu [23] | RS | NS, ORF1ab, N | 59 | 5 Severe | ORF1ab | 13 | Nasopharyngeal | 11.0 | NA | 11.0 | 2.6 | 18.3 | 8.4 | 18.0 | 8.4 |
| 13  | Huang [22] | RS | > 40 ORF1ab, N | 59 | 5 | Severe | ORF1ab | 13 | Nasopharyngeal | 11.0 | NA | 11.0 | 2.6 | 18.3 | 8.4 | 18.0 | 8.4 |
| 14  | Kujawski [24] | Case series | NS | 53 | 0 | Mild | None | 10 | Sputum | 18.1 | 4.8 | 17.3 | 5.2 | 20.0 | 4.0 | 17.3 | 5.2 |

(continued on next page)
| No. | Author               | Design               | Gene                        | Age* | Clinical severity | Reported Treatment | Size | Sampling Location | 2 consecutive negatives Day -1 Mean | SD | 2 consecutive negatives Last positive Mean | SD | Recurrence Day -1 Mean | SD | Recurrence Last positive Mean | SD |
|-----|----------------------|----------------------|-----------------------------|------|-------------------|-------------------|------|-------------------|-------------------------------------|----|------------------------------------------|----|----------------------------------|----|----------------------------------|----|
| 15  | Lee [37]             | Case series          | NA, Rdrp, E, N              | 46   | Moderate          | AV                | 1    | Stool             | 16.9                               | 7.1 | 13.5                                     | 4.3 | 18.0                             | NA | 18.0                             | NA |
| 16  | Leschke [25]         | Case series          | Cl ≥ 43 Rdrp, Rdrp, E, ORF3a| 38.5 | Mild              | None              | 4    | Nasopharyngeal    | 19.0                               | NA | 6.0                                      | NA | 18.0                             | NA | 18.0                             | NA |
| 17  | Lim [30]             | Case series          | Cl ≥ 40 Rdrp, E, Rdrp, E    | 54   | Mild              | L/R + other       | 1    | Sputum            | 10.0                               | NA | 10.0                                     | NA | 16.0                             | NA | 16.0                             | NA |
| 18  | Li [19]              | Case series          | Cl > 36 Rdrp, E, Rdrp, E    | 42.5 | Mild              | L/R + aIFN        | 5    | Nasopharyngeal    | 12.4                               | 3.8 | 12.2                                     | 6.5 | 8.0                              | NA | 8.0                              | NA |
| 19  | Marchand-Seneca [38] | Case series          | Cl ≥ 0 AV, ORF1             | 56   | Moderate          | NS                | 4    | Blood             | 15.6                               | 3.5 | 15.6                                     | 3.5 | 6.0                              | NA | 6.0                              | NA |
| 20  | Pongpirul [14]       | Case series          | Cl ≥ 0 AV, ORF1             | 60   | Mild              | Antimicrobials    | 1    | Nasopharyngeal    | 16.5                               | 9.3 | 16.5                                     | 9.3 | 8.0                              | NA | 8.0                              | NA |
| 21  | Scott [39]           | Case series          | CDC                          | 26   | Mild              | None              | 1    | Sputum            | 18.0                               | NA | 8.0                                      | NA | 16.0                             | NA | 16.0                             | NA |
| 22  | Tan [26]             | RS                   | NS                           | 7    | Mild              | NS                | 3    | Sputum            | 15.0                               | 1.7 | 14.3                                     | 1.2 | 17.5                             | 7.8 | 16.5                             | 6.0 |
| 23  | Tan [40]             | Case series          | Cl ≥ 45 ORF1                | 73   | Moderate          | Yes, NS           | 2    | Stool             | 14.5                               | 6.0 | 13.5                                     | 6.0 | 15.0                             | NA | 15.0                             | NA |
| 24  | Thevarajan [41]      | Case series          | Cl ≥ 45 E                   | 47   | Severe            | NS                | 1    | Rectal            | 22.0                               | NA | 22.0                                     | NA | 6.0                              | NA | 6.0                              | NA |
| 25  | Woeifel [7]          | Case series          | < 10³ copies/mL             | Adult| Mild              | None              | 8    | Sputum            | 16.9                               | 4.9 | 16.9                                     | 4.9 | 11.2                             | 3.4 | 11.2                             | 3.4 |
| 26  | Wu [8]               | Case series          | Cl ≥ 45 ORF1                | 41   | Moderate          | AV (88%), aIFN    | 1    | Faeces            | 15.2                               | 5.9 | 15.2                                     | 5.9 | 26.7                             | 12.3 | 26.7                             | 12.3 |
| 27  | Xu [16]              | Prospective          | Cl ≥ 45 ORF1                | 4.8  | Mild              | aIFN              | 33   | Nasopharyngeal    | 14.9                               | 5.7 | 14.9                                     | 5.7 | 15.4                             | 5.4 | 15.3                             | 5.5 |
| 28  | Young [9]            | Case series          | Cl ≥ 38 N, ORF1ab           | 37   | Mild              | None              | 3    | Stool             | 15.2                               | 5.5 | 15.2                                     | 5.5 | 6.7                              | 0.6 | 6.7                              | 0.6 |
| 29  | Yu [10]              | RS                   | Cl ≥ 38 N, ORF1ab           | 56   | Moderate          | L/R (5/6)         | 4    | Nasopharyngeal    | 15.1                               | 5.0 | 15.1                                     | 5.0 | 15.1                             | 5.0 | 15.1                             | 5.0 |
| 30  | Zhang [11]           | Case series          | Cl ≥ 38 N, ORF1ab           | 37   | Mild              | None              | 17   | Nasopharyngeal    | 18.0                               | 11.3 | 18.0                                     | 11.3 | 20.0                             | 8.5 | 20.0                             | 8.5 |
| 31  | Zheng [12]           | RS                   | Cl ≥ 38 N, ORF1ab           | 47   | Mild              | None              | 21   | Nasopharyngeal    | 17.0                               | 6.1 | 17.0                                     | 6.1 | 17.0                             | 6.1 | 17.0                             | 6.1 |

(continued on next page)
The average duration of positive SARS-CoV-2 viral detection (Day -1) from URT specimens ranged from 7.9 days to 20 days after symptom onset in mild adult patients, and from 6 to 30.8 days in moderate-severe patients. The average duration of positive SARS-CoV-2 viral detection from LRT specimens ranged from 8 days to 38.4 days after symptom onset in mild adult patients, and from 6 days to 26.9 days in adults with moderate-severe symptoms. In children with mild COVID-19 symptoms, average duration of positive SARS-CoV-2 viral detection ranged from 5.7 days to 17 days after symptom onset in the URT and was reported as 13 days in the LRT in one study [17]. Duration of positive SARS-CoV-2 viral detection in children with moderate symptoms was observed in two studies reporting viral detection for 8 days and 14.5 days after symptom onset in the URT [17,26]. Furthermore, several studies have reported positive SARS-CoV-2 viral detection in the faeces and blood in adults, and in faeces only in children. One adult patient was reported to have viral positivity in ocular fluids, whereas other studies did not find evidence of positive SARS-CoV-2 viral detection in the eye [29]. Only one adult patient was reported to have a positive viral sample in the urine [22].

Recurrence of viral positivity after two consecutive negative tests were observed, was observed in 7 out of 37 studies. Recurrence of positivity occurred in adult patients and URT specimen with mild symptoms (1 patient in LRT), and in mild-severe adult patients and URT, LRT and faecal specimen.

However, the actual risk of a reinfection with SARS-CoV-2 after confirmed negativity remains to be elucidated. Among the seven studies which reported recurrence of viral positivity, five studies reported only sporadic cases which are most likely a technical false-positive due to the short time between SARS-CoV-2 negativity and reinfection and lack of validation of viral positivity with a second test [9,13,20,30,31]. In contrary, in two studies the duration of recurred positivity of SARS-CoV-2 was reported to last for approximately 2 weeks after having a confirmed negative test, implying true recurrence [17,22]. However, as these studies did neither capture the antibody response nor reported clinical signs throughout the study and in the follow-up period, the clinical significance of the observed recurred viral positivity cannot be unambiguously determined.

Generally, the average duration of viral detection only differed minimally when setting the final day as Day -1 of first negative test (results described in text above) or as day of last positive test in the above patient populations.

### 3.3. Aggregation of study data

We then aggregated the data of 22 selected studies to report a pooled estimate of the duration of positive SARS-CoV-2 viral detection. We report the weighted mean for both outcome measures, negative conversion defined by obtaining two consecutive negative samples and negative conversion after recurrence (positive sample was detected after two consecutive negatives were obtained). As sampling frequency varied and was not daily for all the studies, we also report the results obtained when setting different endpoint measures: 1) final day of positive detection of virus is day -1 of first negative of two consecutive measurement and 2) final day of positive detection of virus is the day on which last positive test was obtained, in case Day -1 and last positive day were not identical, to avoid introducing predictions into the outcome measures. Notably, there was a portion of patients that did not reach viral negativity within the time of sampling for which we reported the day of the last positive test as final day. Considering studies that were included in the aggregation analysis, the share of mild patients (children and adults) that did not reach negativity were 27/139 for URT specimen, 6/52 for LRT specimen and 26/45 for faecal specimen. Regarding moderate-severe patients (children and adults), these were 14/154 for URT specimen, 6/112 for LRT specimen, 0/38 for blood specimen and 10/110 for faecal specimen. For the overall patient population, the patients that did

| No. | Author          | Design     | Age | Clinical severity | Threshold Cycle | Gene | Size | Sampling location | Reported Treatment | Time of follow-up | Sampled specimen(s) |
|-----|----------------|------------|-----|-------------------|-----------------|------|------|-------------------|--------------------|-------------------|-------------------|
| 22  | Zhou [18]      | Case series | < 50 | Severe            | ≥ 40            | NCOV | 5/11 | URT               | Oral               | 14 days           | URT, LRT, faecal   |
| 32  | Zhou [18]      | Case series | < 50 | Severe            | NCOV            | NCOV | 5/11 | URT               | Oral               | 14 days           | URT, LRT, faecal   |
| 33  | Zhou [18]      | Case series | < 50 | Severe            | NCOV            | NCOV | 5/11 | URT               | Oral               | 14 days           | URT, LRT, faecal   |

The table shows the duration of positive SARS-CoV-2 viral detection in children with mild COVID-19 symptoms. The average duration of positive SARS-CoV-2 viral detection ranged from 5.7 days to 17 days after symptom onset in the URT and was reported as 13 days in the LRT in one study [17]. Duration of positive SARS-CoV-2 viral detection in children with moderate symptoms was observed in two studies reporting viral detection for 8 days and 14.5 days after symptom onset in the URT [17,26]. Furthermore, several studies have reported positive SARS-CoV-2 viral detection in the faeces and blood in adults, and in faeces only in children. One adult patient was reported to have viral positivity in ocular fluids, whereas other studies did not find evidence of positive SARS-CoV-2 viral detection in the eye [29]. Only one adult patient was reported to have a positive viral sample in the urine [22].

Recurrence of viral positivity after two consecutive negative tests were observed, was observed in 7 out of 37 studies. Recurrence of positivity occurred in adult patients and URT specimen with mild symptoms (1 patient in LRT), and in mild-severe adult patients and URT, LRT and faecal specimen.

However, the actual risk of a reinfection with SARS-CoV-2 after confirmed negativity remains to be elucidated. Among the seven studies which reported recurrence of viral positivity, five studies reported only sporadic cases which are most likely a technical false-positive due to the short time between SARS-CoV-2 negativity and reinfection and lack of validation of viral positivity with a second test [9,13,20,30,31]. In contrary, in two studies the duration of recurred positivity of SARS-CoV-2 was reported to last for approximately 2 weeks after having a confirmed negative test, implying true recurrence [17,22]. However, as these studies did neither capture the antibody response nor reported clinical signs throughout the study and in the follow-up period, the clinical significance of the observed recurred viral positivity cannot be unambiguously determined.

Generally, the average duration of viral detection only differed minimally when setting the final day as Day -1 of first negative test (results described in text above) or as day of last positive test in the above patient populations.

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We then aggregated the data of 22 selected studies to report a pooled estimate of the duration of positive SARS-CoV-2 viral detection. We report the weighted mean for both outcome measures, negative conversion defined by obtaining two consecutive negative samples and negative conversion after recurrence (positive sample was detected after two consecutive negatives were obtained). As sampling frequency varied and was not daily for all the studies, we also report the results obtained when setting different endpoint measures: 1) final day of positive detection of virus is day -1 of first negative of two consecutive measurement and 2) final day of positive detection of virus is the day on which last positive test was obtained, in case Day -1 and last positive day were not identical, to avoid introducing predictions into the outcome measures. Notably, there was a portion of patients that did not reach viral negativity within the time of sampling for which we reported the day of the last positive test as final day. Considering studies that were included in the aggregation analysis, the share of mild patients (children and adults) that did not reach negativity were 27/139 for URT specimen, 6/52 for LRT specimen and 26/45 for faecal specimen. Regarding moderate-severe patients (children and adults), these were 14/154 for URT specimen, 6/112 for LRT specimen, 0/38 for blood specimen and 10/110 for faecal specimen. For the overall patient population, the patients that did
not clear within the sampling time accounted for 14% of the whole dataset.

We aggregated the data of selected studies to report a weighted mean of duration of positive SARS-CoV-2 viral detection in both URT, LRT, and faeces for mild and moderate-severe patients. We chose to display the results of the aggregated data for which the final day was set as Day -1 of first negative in the main text of this manuscript, as this is the most conservative approach (Figs. 2 and 3). Also, the result of this measure differed only marginally to the result defining the final day as last positive (maximum 1 Day). The pooled estimates for all data groupings, including recurrence, can be found in the supplementary Table S5.

In total we included data from 650 patients in this analysis. Notably, a high heterogeneity (I² > 80%/C0 90%) was observed in the majority of the subgroup analysis indicating that these data should be interpreted cautiously and only considered as trends. Significant publication bias was found by Egger test only for the subgroup of adult, mild patients with URT specimen (p < 0.05).

In mild adult patients, the pooled estimate of the mean duration of positive SARS-CoV-2 viral detection after symptom onset in the

Table 3
Summary of studies describing duration of viral detection as days after hospitalization.

| No | Author | Design | Threshold Gene | Age | Clinical severity | Reported Treatment | Size | Sampling Location | 2 Consecutive negatives Day -1 Mean | 2 Consecutive negatives Last positive Mean |
|----|--------|--------|----------------|-----|------------------|-------------------|------|------------------|-----------------------------------|-------------------------------------------|
| 34 | Chen [42] | Retrospective | WHO | 51 0 | Mild | NS | 2 | Pharyngeal | 45 | 21 |
| 35 | Lo [43] | Case series | Ct > 38 | 54 0 | Mild | L/R | 2 | Faeces | 16 | 7 |
| 36 | Xing [44] | Case series | ORF1ab, N | 5 0 | Mild | allIFN +Ribavirin | 3 | Throat | 18 | 7 |
| 37 | Xu [46] | Case series | ORF1ab, N | 51 0 | Mild | NS | 47 | Throat | 11 | 4 |

No recurrence was reported for these studies. Blank columns apply if sampling was daily (value of Day -1 equals last positive) or no recurrence occurred.

aIFN: Alpha interferon, Ct = Threshold cycle, L/R: Lopinavir/Ritonavir, N: Truncated nucleocapsid, ORF: Open reading frame, SD: Standard deviation, WHO: World health organization; * Age displayed as median in years

Fig. 2. Forest plots of selected aggregations reporting weighted means of duration of viral detection as days after symptom onset in adults. Pooled estimate for (a) all mild patients (non-treated and treated) and URT specimens, (b) all moderate-severe patients and URT specimen, (c) all mild patients and LRT specimen, (d) all moderate-severe and LRT specimen, (e) all mild patients and faecal specimen, (f) moderate-severe and faecal specimen and (g) moderate-severe patients and blood specimen. The forest plots include data that describe duration of viral detection defining the final day as day -1 of first negative day of two consecutive negatives. CI: Confidence Interval; D-1: Day -1 of first negative test of two consecutive; FCS: Faeces, LRT: Lower respiratory tract, SE: Standard error, URT: Upper respiratory tract. Numbers in brackets refer to listing in reference list.
URT was 12-1 days (CI: 10-12, 14-05) (Fig. 2a), 24-1 days (CI: 10-02, 38-19) in LRT (Fig. 2c), and 15-5 days (CI: 8-04, 22-88) in faeces (Fig. 2e). There was only one study describing duration of viral detection in the blood (17-1 days) in mild adult patients [12].

In moderate-severe adult patients, the pooled estimate of mean duration of positive SARS-CoV-2 viral detection after symptom onset in the URT was 15-8 days (CI: 11-12, 20-56) (Fig. 2b), 23-2 days (CI: 21-49, 24-97) in the LRT (Fig. 2d), 20-8 days (CI: 16-40, 25-17) in faeces (Fig. 2f), and 13-3 days (CI: 7-35, 19-22) in blood (Fig. 2g).

In children with mild symptoms, the pooled estimate of the mean duration of positive SARS-CoV-2 viral detection after symptom onset was 11-1 days (CI: 7-14, 15-11) in URT and 16-0 days (CI: 11-49, 20-47) in the faeces (Fig. 3a and b). No viral detection was reported in the blood for children.

We then directly compared the duration of viral detection of URT and LRT specimen in each patient per study. Regarding mild adult patients, only one study sampled both URT and LRT specimen in the same patient and found that the mean difference of viral detection of SARS-CoV-2 in URT compared to LRT is ~5-7 days (SD: 4 days) (7). Regarding moderate-severe adult patients, the pooled estimate of the mean difference of duration of positive SARS-CoV-2 viral detection in URT compared to LRT was ~5-9 days (CI: ~9-40, ~2-32) (see Fig. 4). For children, a direct comparison was not performed due to lack of data.

Generally, the mean duration of positive SARS-CoV-2 viral detection accounting for recurrence of positivity did not differ substantially in mild adults or children (if different, less than 1 Day difference). But, in moderate-severe patients the pooled estimate of the mean duration of positive SARS-CoV-2 viral detection was on average approximately 3-4 days longer for LRT specimen and 1-2 days for faeces, accounting for recurrence of viral positivity (see Table 55).

### 3.4. Spatial and temporal dynamics of viral RNA load

To investigate whether the viral RNA load differs between disease severity and sampling location, we combined data from four published studies and analysed the viral RNA load per patient as a function of time, stratified after clinical severity (mild and moderate-severe) and location of sampling (URT, LRT and faeces) (Fig. 5). No quantitative viral data was available for children and only one study reported limited quantitative data of blood specimen (four data-points) [20].

In mild patients, viral RNA load was highest during the first week in the URT having a maximum viral RNA load of ~6-61 × 10^6 viral copies/mL on Day 4, whereas the maximum viral RNA load reported for LRT was ~2-69 × 10^6 copies/mL on Day 6 (Table 4 and Fig. 5a vs. b). The maximum viral RNA load in faeces was reported as ~3-55 × 10^7 copies/mL on Day 9 in mild patients (Fig. 5c). The average viral RNA load was found to be significantly higher in LRT relative to URT in the Woelfell et al. study (t test, q < 0-001) (Fig. 6) [7]. However, as this was the only study which allowed this comparison, additional studies of quantitative viral dynamics are needed to assess the viral RNA load of the URT compared to LRT.

In moderate-severe patients, the maximum viral RNA load was reported as 4-60 × 10^8 copies/mL on Day 8 in URT and 3-45 × 10^8 copies/mL on Day 11 in LRT (Table 4, Fig. 5d vs. e). Maximum viral RNA load in faeces was shown to be 2-76 × 10^8 copies/mL on Day 18 and 1 × 10^8 copies/mL on Day 3 in blood specimen (Table 4). No significant difference was found in the average viral RNA load comparing URT and LRT samples in this disease population.

### 4. Discussion

In this study we conduct a systematic review of the spatial and temporal viral dynamics of SARS-CoV-2 stratified after age and clinical severity. We report the per study data of duration of viral detection and viral RNA load over time, but also show pooled estimates of these, providing a better basis for interpretation. While viral tropism likely extends beyond the specimens described in this study, the lack of data on viral RNA load from other locations has limited our analysis to faeces, blood, URT and LRT [32].

Additionally, this study has several limitations which need to be considered. First, different genes and thresholds were used to assess
negative conversion of SARS-CoV-2 hampering the direct comparison of studies. Second, the classification of clinical symptoms into the severity categories, mild, moderate, severe was based on different guidelines across the studies and we were not able to unify and verify all (mostly due to missing individual symptom data). Third, studies that only reported fractions or median of duration of viral shedding were excluded, which might introduce a selection bias into this review. Fourth, the viral RNA load was measured via RT-PCR, which cannot differentiate dead virus particle, and hence data presented here might not necessarily reflect active viral replication, which is likely of shorter duration. However, this technique is currently used worldwide to measure the quantities of SARS-CoV-2. Fifth, a portion of the patients included in this review (14 %) did not clear the virus in the time frame of sampling and were not followed until clearance of infection, hence the here presented data might be an underestimation of the duration of virus detection which might introduce a

**Table 4**

Summary of maximum viral RNA load per location and COVID19 clinical severity

| Author | URT | LRT | Faeces | Blood |
|--------|-----|-----|--------|--------|
| Woelfel et al. [7] | ~6.61 × 10⁶ on Day 4 (6.66 × 10⁶ in publ.) | ~2.69 × 10⁸ on Day 6 (7.11 × 10⁸ copies/swab in publ.) | ~3.55 × 10⁷ on Day 9 | ND |
| Zou [13] | ~2.19 × 10⁷ on Day 4 | ND | ND | ND |
| G. Lui et al. [20] | 2.50 × 10⁶ on Day 4 | ND | 7.94 × 10⁵ on Day 7 | ND |
| Zheng et al. [12] | ND | ~2.00 × 10⁷ on Day 11 | ND | ND |
| Moderate-Severe | | | | |
| Woelfel et al. [7] | ND | ND | ND | ND |
| Zou [13] | ~1.32 × 10⁷ on Day 5 | ND | ND | ND |
| G. Lui et al. [20] | 4.60 × 10⁶ on Day 8 | 3.45 × 10⁷ on Day 11 | 2.76 × 10⁶ on Day 18 | 1 × 10⁶ on Day 3 |
| Zheng et al. [12] | ND | ~1.82 × 10⁷ on Day 4 | ND | ND |

LRT: Lower respiratory tract, ND: Not determined, URT: Upper respiratory tract;
* all subjects in this study received Lopinavir/Ritonavir; 
* estimated data as digitalized from graph. Number in brackets refer to listing in reference list.
reporting bias in the outcome measure. Sixth, only a selection of studies investigated the duration of SARS-CoV-2’s positivity in more than one location, e.g., LRT sampling was more often performed in moderate-severe patients than mild patients, which might further introduce a bias in the reported outcome measure. Also, it further limits the direct comparison of duration of viral detection in LRT relative to URT samples on a per patient level to only specific disease severities and age groups. Finally, our aggregation analysis exhibited a high heterogeneity ($I^2 \sim 80–90\%$) and included too few studies to make statements about statistical significance, which highlights that these data should be interpreted cautiously and only considered as trends. There are several variables that could explain the high heterogeneity of data: first, there was no uniform cycle threshold (Ct) value of one distinct gene used to define negativity of SARS-CoV-2 across the studies; second, different RT-PCR/RNA extraction kits were used (if reported) for sample analysis; thirdly, samples were combined to LRT and URT specimen which might mean that the analysis misses granularity regarding specific subgroups of sampling locations. However, given the lack of big data sets, these three points are still not uniformly defined across currently ongoing studies highlighting the complexity of having a universal defined viral endpoint.

Regardless of these limitations, some trends can be extracted from this analysis. Firstly, we consistently find that SARS-CoV-2 is detected in LRT, URT and faecal specimens, irrespective of clinical severity of disease. Second, our data indicates that the duration of detection of SARS-CoV-2 is longer in LRT than in URT in adult patients. Third, there seems to be little difference in the duration of detection of SARS-CoV-2 in mild patients as opposed to moderate-severe patients in the LRT, but an indication of longer duration of viral detection in faeces and the URT for moderate-severe patients was shown. Fourth, viral RNA load in URT peaks within the first week of infection, whereas viral RNA load in LRT and faeces within the second week of infection.

In conclusion, we believe that this systematic review and meta-analysis can support refinement of mathematical modelling as well as aid in the definition of appropriate endpoints for clinical trials testing therapeutic intervention aimed at reducing viral RNA load of SARS-CoV-2. Furthermore, it highlights the importance of testing for viral presence in the LRT, which may clear more slowly compared to the URT.

5. Research in context

5.1. Evidence before this study

The temporal and spatial dynamics of SARS-CoV-2 have been mainly summarized in case series and retrospective studies. We systematically searched PubMed/MEDLINE and Cochrane review database for studies published between 1. November 2019 and 23rd of April 2020 using SARS-CoV-2 [MESH] OR “COVID 19 [MESH]” alone, or in combination with “virology” OR “viral” OR “Epidemiology” AND “clinical as search terms. We included studies that reported individual viral data over time measuring negative conversion by two consecutive negative tests, individual clinical severity, and age. We excluded studies that reported viral data as patient fraction, reported only baseline data, included solely asymptomatic patients or were interventional studies. Extracted data included author, title, design, sample size, thresholds and genes of RT-PCR, patient age, COVID-19 severity, clinical characteristics, treatment, location of viral sampling, duration of viral detection, and viral load. We pooled the data of selected studies to determine effect estimates of duration of viral detection and conducted subgroup analyses per disease severity and age. Viral load was visualized over time.

5.2. Added value of this study

Our analysis demonstrated consistent viral detection from specimens from the URT, the LRT, and faeces in patients with mild and moderate-severe COVID-19. We showed that SARS-CoV-2 persists for a longer duration in the LRT compared to the URT in moderate-severe and mild adult patients. However, we found that the duration of viral detection between mild and moderate-severe adult patients is similar in the LRT. But, an indication of longer duration of viral detection in faeces and the URT for moderate-severe patients was shown. Further, viral load was demonstrated to peak in the URT within first
week of infection, whereas maximum viral load has been observed to occur later and within the second week of infection in the LRT.

5.3. Implications of all the available evidence

This systematic review and meta-analysis can support the improvement of mathematical modelling of SARS-CoV-2's infection as well as aid in the definition of appropriate endpoints for clinical trials which are testing therapeutic intervention aimed at reducing viral load of SARS-CoV-2.

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Author contribution

A.W. and M.O.A.S wrote the manuscript and conceived the study. M.J. and M.O.A.S. provided input to the analysis and interpretation of study. A.W. analysed the data. All authors reviewed the manuscript.

Declaration of Competing Interest

A.W., M.J., and M.S. have nothing to disclose.

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Supplementary material

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.ebiom.2020.102916.

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