

Towards a sensitive and accurate interpretation of molecular testing for SARS-CoV-2: a rapid review of 264 studies

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Abstract

Background

Sensitive molecular diagnostics and correct test interpretation are crucial for accurate COVID-19 diagnosis and thereby essential for good clinical practice. Furthermore, they are a key factor in outbreak phases where active case finding in combination with isolation and contact tracing are crucial for outbreak control.

Aim

As more countries are on the brink to enter new phases in the COVID-19 outbreak response, we reviewed current published knowledge on the kinetics of SARS-CoV-2 RNA molecular detection in a wide range of clinical samples to support the laboratory response and to inform Public Health control.

Methods

We performed an extensive search on studies published between 1 December 2019 and 15 May 2020, reporting on SARS-CoV-2 molecular detection and/or virus isolation in any laboratory specimens of COVID-19 cases.

Results

We compiled a dataset of 264 studies including 32515 COVID-19 cases, and additionally aggregated data points sampling (n=2777) from 217 adults with known infection timeline. We summarised data on SARS-CoV-2 detection in the respiratory and gastrointestinal tract, blood, oral fluid, tears, cerebrospinal fluid, peritoneal fluid, semen, vaginal fluid; where provided, we also summarised specific observations on SARS-CoV-2 detection in pregnancy, infancy, children, adolescents and immunocompromised individuals.

Conclusion

Optimal SARS-CoV-2 molecular testing relies on choosing the most appropriate sample type, collected with adequate sampling technique, and with the infection timeline in mind. We outlined knowledge gaps and directions for future well-documented systematic studies.

Keywords

SARS-CoV-2, COVID-19, Laboratory Diagnosis, Polymerase Chain Reaction

Introduction

In 2019 a novel human pathogenic coronavirus, SARS-CoV-2, emerged in Wuhan, China [1], leading to a worldwide outbreak, declared a public health emergency of international concern on 30 January 2020 [2] and a pandemic on 11 March 2020 [3].

SARS-CoV-2 is a positive-stranded RNA virus from the species Severe acute respiratory syndrome-related coronavirus, *Sarbecovirus* subgenus, genus *Betacoronavirus*, family *Coronaviridae*. The species contains a wide range of bat and human viruses including SARS-CoV that caused an outbreak in 2002/2003. The SARS-CoV-2 origins are still unknown, but zoonotic transmission, with bats (in particular *Rhinolophus* spp.) as the probable primary reservoir and other animals as intermediate hosts, is considered the most likely route [4, 5].

In the context of the current pandemic, rapid and reliable laboratory diagnosis is essential for detection, confirmation, and ruling out of cases, clinical management and hospital infection prevention measures, source and contact tracing, and (lifting of) isolation measures. Laboratory testing plays a critical role in surveillance to guide public health response. Nucleic acid amplification tests became the first line of COVID-19 testing recommended by WHO [6]. Serological tests are increasingly being implemented [7, 8].

Here, we reviewed the current knowledge on the laboratory aspects of COVID-19 diagnostics with a focus on SARS-CoV-2 molecular assays to support the laboratory response for clinical case management and to inform Public Health control.

Methods and search results

We searched repetitively Pubmed, medRxiv and bioRxiv with keyword “coronavirus” limiting to results published between 1st December 2019 and 15th May 2020 and screened the titles and brief description of >8700 publications in total. We identified studies on SARS-CoV-2 (incl. name variations like “novel coronavirus”, “2019-nCoV”) in humans (all ages), written in English, Chinese or French, and excluded reviews, viewpoints, or news. We selected studies using the words “detection”, “testing”, “PCR”, “viral load”, “viral kinetics/dynamics/clearance/shedding”, “isolation”, “persistence”, “samples”, “bodily fluids”, “diagnosis”, “case report/series”, “case(s)”, “cluster”, “transmission”, “patients”, “neonate”, “child(ren)”, “pregnant”, “clinical characteristics/findings/manifestations/features/outcomes”, “infection”, “pneumonia”, “asymptomatic” in the title, brief description or abstract (if available) aiming to narrow down to clinical reports. This yielded 702 publications for in-depth abstract and full-text screening. Additionally, we scanned literature cited in these articles as well as suggested similar publications and COVID-19 resource collections on the publishers’ websites. Finally, we included 264 studies reporting on SARS-CoV-2 molecular detection and/or virus isolation in any laboratory specimens of COVID-19 cases. We excluded reviews, meta-analyses, news, guidelines, or modelling studies based on public data.

We aimed to summarize the current information on SARS-CoV-2 kinetics in relation to clinical syndrome, in different bodily fluids, while also noting any specifics in vulnerable groups (pregnant women, children and immunocompromised individuals). We extracted data on cases’ demographics (number of adults, children, pregnant and immunocompromised individuals; age; sex; severity of disease) and specimens tested for SARS-CoV-2 (number of patients with collected respiratory, gastrointestinal and blood sampling, oral fluid, tears, urine, cerebrospinal fluid, semen, vaginal fluid, breast milk and perinatal samples; all incl. sample types tested by PCR and virus cultures where available; number of patients with sequenced samples) and compiled a dataset containing 32515 COVID-19 cases (Supplementary Dataset). Even though nasopharyngeal swabs are the routine respiratory sample for viral infections, we also included publications with nasal/midturbinare swabs or those using the term “nasal” indiscriminately when describing nasopharyngeal swab collection technique. Where possible, we noted duplicate case reports in different publications. Due to varying disease severity definitions, we opted for a simplified approach: patients with symptoms or clinical course described as mild, moderate, common, typical, are referred to as “mild”; while severe, critically ill and/or admitted to intensive-care units (ICU), as “severe”. Additionally, we aggregated data from 217 adults with data points from 2777 samples with known collection day post symptoms onset (dps) (Figure 1, Figure 2, Table, and Supplementary Table).

Figure 1 . COVID-19 aggregated RT-PCR results in different sample types (n=2777) by days post symptoms onset in patients (n=217) with mild or severe symptoms.

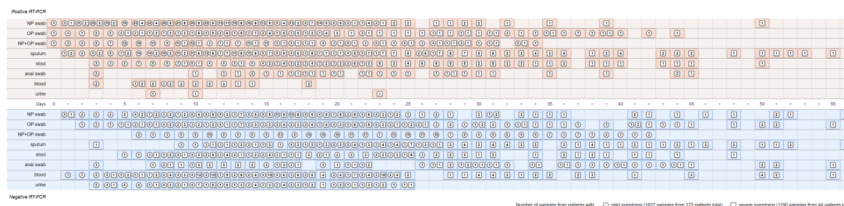


Figure 1: This is a caption

NP: nasopharyngeal; OP: oropharyngeal.

Figure legend: The number of samples with and without detectable SARS-CoV-2 RNA are aggregated by sample type, collection day post symptoms onset (dps) and disease severity. Sampling for patients with symptoms or clinical course described in the original publications as mild, moderate, common, or typical are shown in circles: a total of 1627 samples from 173 adults. Sampling for severe or critically ill and/or admitted to the ICU are shown in squares: a total of 1150 samples from 44 adults. Asymptomatic patients were excluded. Sample types are as follows: NP swab (nasopharyngeal/midturbinare/nasal swab), OP swab (oropharyngeal/throat swab), NP+OP swab (both swabs collected in one tube or results published aggregated), sputum (induced/spontaneous sputum), stool, anal swab (anal/rectal swab), blood (serum, plasma, whole blood or not specified), urine. Sample collection dps are shown as stated by the authors, and if unavailable extracted from timeline descriptions.

Figure 2. Heatmaps of mild and severe laboratory confirmed COVID-19 cases (n=217) with positive and negative RT-PCR results in different sample types (n=2777) by days post symptoms onset.

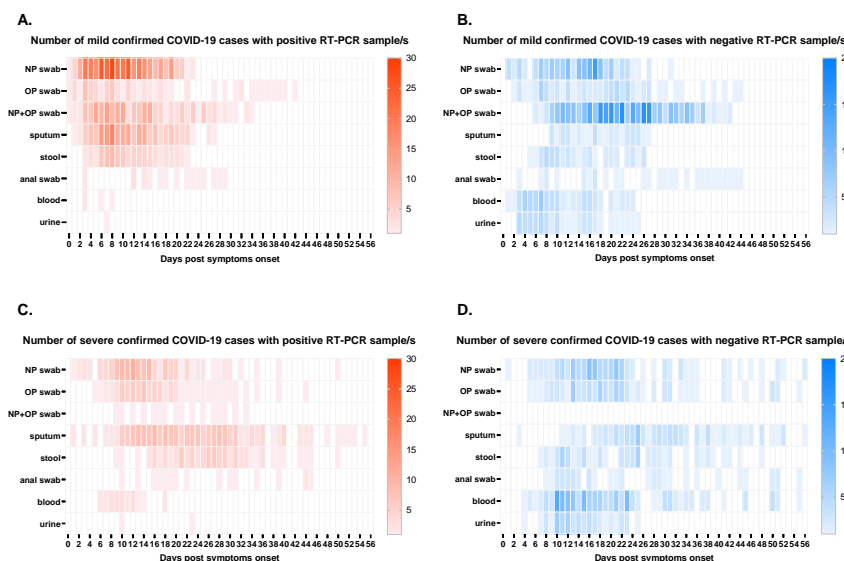


Figure 2: This is a caption

NP: nasopharyngeal; OP: oropharyngeal.

Figure legend: Laboratory confirmed COVID-19 cases (n=217) are grouped by disease severity: those with symptoms or clinical course described in the original publications as mild, moderate, common, or typical (n=173 adults) are referred to as “mild cases” (A. and B.), while those with severe disease or critically ill and/or admitted to the ICU (n=44 adults) are referred to as “severe cases” (C. and D.). Asymptomatic patients were excluded. The cumulative number of cases with respective positive (A. and C) or negative (B and D.) RT-PCR results on different sample types (a total of 1627 and 1150 samples from mild and severe cases respectively) on a respective day post symptoms onset are represented using a colour gradient. Sample types are as follows: NP swab (nasopharyngeal/midturbinate/nasal swab), OP swab (oropharyngeal/throat swab), NP+OP swab (both swabs collected in one tube or results published aggregated), sputum (induced/spontaneous sputum), stool, anal swab (anal/rectal swab), blood (serum, plasma, whole blood or not specified), urine. Sample collection by days post symptoms onset are shown as stated by the authors, and if unavailable extracted from timeline descriptions.

Table . COVID-19 aggregated RT-PCR results in different sample types (n=2777) in patients (n=217) with mild or severe symptoms

	Positive results	Positive results	Positive results	Negative results	Negative results
Sample type	Samples, n	Mild cases, n	Severe cases, n	Samples, n	Mild cases, n
NP swab	461	56	20	254	11
OP swab	151	29	14	165	9
NP+OP swab ^a	197	64	1	296	3
All URT swabs	809	149	35	715	23
Sputum	376	36	23	131	0
Stool	172	14	11	112	11
Anal swab	34	5	6	71	8
All GIT samples	206	19	17	183	19
Blood	26	3	6	222	25
Urine	3	1	1	106	26

NP: nasopharyngeal/midturbinate/nasal; GIT: gastrointestinal tract; OP: oropharyngeal/throat; URT: upper respiratory tract.

^aBoth swabs collected in one tube or results published aggregated

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Stanoeva et al Suppl Dataset until 15052020.xlsx available at <https://authorea.com/users/335799/articles/461602-towards-a-sensitive-and-accurate-interpretation-of-molecular-testing-for-sars-cov-2-a-rapid-review-of-264-studies>

SARS-CoV-2 kinetics and shedding in bodily fluids

Respiratory shedding

Key points

- * SARS-CoV-2 replication in the throat and diagnostic use of upper respiratory tract sampling in the early infection days (regardless of the severity of symptoms)
- * Viral RNA loads peak within the first infection days in the upper and later in the lower respiratory tract; need for standardisation of viral load testing and reporting
- * SARS-CoV-2 RNA detectable from respiratory samples up to 6 weeks in mild and 8 weeks in severe cases, and beyond symptoms resolution
- * Insufficient systematic comparisons between all respiratory samples' types; higher viral loads in sputum than swabs, nasopharyngeal swabs more sensitive than oropharyngeal swabs
- * CT findings could sometimes precede viral RNA detection in the upper respiratory tract and full clinical presentation should always be evaluated

We reviewed 262 studies with respiratory sampling for [?]31957 COVID-19 cases, including data on nasopharyngeal/midturbinat/nasal (NP) swabs ([?]13286 cases), oropharyngeal/throat (OP) swabs ([?]7301), combined NP and OP swabs ([?]1493), sputum ([?]409), bronchoalveolar lavage fluid ([?]21), and other respiratory specimens (endotracheal aspirate, bronchoalveolar swab, [?]21) (Supplementary Dataset) [1, 9-255][256-268].

Lower respiratory tract (LRT) bronchoalveolar lavage (BAL) sampling allowed the initial and subsequent virus culture of SARS-CoV-2 [1, 11, 13]. Almost all BAL specimens described in peer-reviewed literature had detectable viral RNA regardless sampling timing, disease severity or co-morbidities and were useful for ultimate confirmation of difficult cases [11, 44, 71, 77, 78]. Virus isolation was successful from NP swabs 2 dps in 2 mild cases (using Vero E6 cells) [120]; NP and OP swabs 4 dps (using Vero CCL-81 cells) [76] in a mild case [63], and also at 4 dps from NP swab and nasopharyngeal aspirate in another mild case (using Vero E6 cells) [98]. SARS-CoV-2 was isolated from NP swabs of 2 severe cases 1 and 10 dps [135]. In a German study of 9 mild COVID-19 cases, SARS-CoV-2 was isolated up to 8 dps from both upper respiratory tract (URT) swabs (16%) and sputum samples (83%) with viral loads (VL) >106 copies/ml. Furthermore, the authors detected viral subgenomic messenger RNAs (sgRNA) which led them to conclude there was ongoing viral replication in the throat up to 5 dps. Sequencing data also showed the continuous presence of two genotypes of SARS-CoV-2 differing by a single mutation in the throat and lungs samples of a patient [131]. La Scola and colleagues cultured 174 NP swabs and 9 sputum samples testing positive via PCR (from 155 patients total) and succeeded with virus isolation from 129 samples (124 with observable cytopathic effect on Vero E6 cells). They observed a strong correlation between Ct values and virus isolation: 100% isolation rates from samples with Ct 13-17 decreasing to 12% at Ct=33 and no isolation from samples with Ct[?] 34 [211]. An Indian study was successful in isolating SARS-CoV-2 (using Vero CCL-81 cells) from respiratory samples in 9 of 12 samples with Ct values ranging 16-25.1 [217].

Despite the growing amount of literature, only two studies documented NP swabs, OP swabs, and sputum, collected sequentially in the same 16 [172] and 49 [240] patients respectively, while 2 studies described an upper respiratory specimen paired with sputum for a total of 11 cases [39, 131]. Nevertheless, we aggregated the data from 32 observational studies with available infection timeline and respiratory sampling for 216 cases [9, 18, 23, 25, 29, 34, 37, 39, 42-45, 58, 59, 63, 72, 85, 98, 111, 116, 120, 131, 134, 158, 160, 171, 172, 176, 187, 197, 206] to provide a summary (Figure 1, Figure 2, Table, and Supplementary Table). SARS-CoV-2 RNA was detected in NP and OP swabs from symptoms onset up to 42 dps in mild cases [158] and 50 dps in severe ones [172]. Sputum yielded positive results up to 27 dps in mild cases [131], but 55 dps in

severely ill [172] (Figure 1 and Figure 2). Several studies reported SARS-CoV-2 RNA detection from the URT for a median period of 10-20 days [53, 59, 79, 99, 105, 187, 191] with a prolonged one seen in severe cases [99, 105, 191]. SARS-CoV-2 RNA was detectable in URT samples well beyond waning of respiratory symptoms [37, 46, 107, 131]. SARS-CoV-2 remained detectable in OP swabs [?]2 weeks, (nine mild cases) and in sputum >3 weeks (six mild cases) despite symptoms resolution [131]. Chen and colleagues described recurring SARS-CoV-2 RNA positivity in OP swabs of a patient until 30 dps (VL 4.56x10² copies/mL), well after pneumonia resolution and hospital discharge [37]. Prolonged viral RNA detection in OP swabs (range 5-30 dps for 22 cases) was also reported for mild cases regardless of symptoms, incl. >3 weeks in 8 cases [199]. They did not study if infectious virus could be detected. Sun and colleagues aggregated data on 175 NP swabs, 88 OP swabs, and 62 sputum samples, and estimated a median/95th percentile time until loss of detection as follows: NP 22.7/46.3 dps, OP 15.6/32.8 dps, and sputum 20/43.7 dps for 43 mild cases vs. NP 33.5/49.4 dps, OP 33.9/53.9 dps, and sputum 30.9/44.7 dps for six severe cases [240].

A Nanchang study (21 mild, ten severe cases) observed clearance in NP swabs within 10 dps in 90% of the mild cases compared to continuous RNA detection >10 dps in all severe cases [99]. Feng and colleagues detected SARS-CoV-2 RNA in NP swabs of 24 mild cases for 16±7 days compared to 22±4 days in eight ICU patients [105]. An aggregation of retrospective observations from 191 hospitalised adults in Wuhan showed a median duration of URT viral RNA detection of 20 (IQR 16-23) dps with continuous detection until death in non-survivors and ranges 8-37 dps in survivors [79]. Another study including 66 COVID-19 cases found a median of 9.5 (6-11) dps until the first negative results in OP swabs [53]. A total of five patients presented with mild symptoms and detectable SARS-CoV-2 RNA 4-15 days following last negative OP swab and previous hospital discharge [104], though the COVID-19 reactivation as reported by the authors could have been prolonged disease course too. Another Wuhan-based study reported re-hospitalisation with mild symptoms for 11 cases within a median of 16 (range 6-27) days, of which four has viral RNA detected in OP swabs [254].

Duration of shedding may be related to patient's general health condition: in a Wuhan-based study 27 out of 56 mild cases had prolonged SARS-CoV-2 RNA detection >24 days in NP/OP swabs, associated with old age and comorbidities. The proportion of positive respiratory samples decreased from 89% to 66%, 32%, 5%, and 0% in weeks 2-6 since symptoms onset [187]. Xu and colleagues summarised respiratory samples data from 113 patients and observed a median RNA detection for 17 (IQR 13-22) dps. Prolonged detection [?]15 dps was associated with males, old age, hypertension, severe illness upon admission, invasive mechanical ventilation, and corticosteroid treatment [150]. A Wuhan-based study on 41 discharged severe cases reported SARS-CoV-2 RNA detection in OP swabs for a median of 31 (IQR 24-40, range 18-48) dps and no significant difference between male and female, nor between cases <65 and [?]65 years [186].

In the studies that provide quantitative results (n = 26), [9, 10, 25-27, 34, 37, 39, 40, 59, 63, 99, 111, 119, 120, 122, 131, 158, 160, 161, 170, 172, 202, 206, 220, 248] the highest VL in URT specimens were reported in the early days of the disease [34, 39, 59, 63, 99, 120, 131, 170, 172], also before development of respiratory symptoms [39, 119, 170]. A study of nine mild cases reported SARS-CoV-2 RNA detection from all NP and OP swabs in the first 5 dps with (average VL 6.76x10⁵ copies/swab and maximum 7.11x10⁸ copies/swab), whereas detection rate in subsequent swabs was only 40% reaching up to 28dps (average VL 3.44x10⁵ copies/swab) [131]. Among four patients (2 mild, 2 severe) viral loads in NP swabs ranged from 7.4 log₁₀ copies/1000 cells (mild case 2 dps) and 7.1 log₁₀ copies/1000 cells (severe case 6 dps) to negative 9-14 dps, while for a critically ill case they were in the range 6.7-4.4 log₁₀ copies/1000 cells and persisted 24 dps until death [120].

He and colleagues reported high VL for 414 OP swabs from 94 patients in the early days of infection and gradual decrease until about 21 dps with no difference when stratified by sex, age, or disease severity [170]. However, VL in the sputum of 22 mild cases reached a peak in week 2 since symptoms onset and were significantly lower than those of 74 severe cases [191]. In a paediatric dialysis unit with 12 COVID-19 cases (6 asymptomatic, 6 mild), the viral loads were significantly higher for the patients with symptoms [212]. Kimball and colleagues reported no significant difference between the Ct values in NP swabs collected

from 10 symptomatic, 10 presymptomatic and 3 asymptomatic cases in a nursing facility [119]. Among 61 healthcare workers, VL of self-collected NP+OP swabs were significantly lower for 56 asymptomatic vs. five symptomatic cases [248]. A study on 12 cases (9 mild, 3 severe) showed that Ct values from respiratory samples were correlated with disease severity scores like ARDS index PaO₂/FiO₂ ratio and lung injury Murray score, as well with biochemical indicators like albumin levels and lymphocytes and neutrophils percentages, and concluded viral loads could be as a COVID-19 severity predictor [17]. In a cohort of 92 cases (51 mild, 11 mild turning severe, 30 severe) low Ct values (high VL) in sputum were correlated with severe COVID-19 and risk of progression to severe disease [202].

Comparing respiratory specimens, higher VL were reported for sputum than respiratory swabs [9, 40, 122, 131, 172]. A study using RT-PCR and droplet digital PCR found both significantly higher positive rates and average VL in sputum (66% and 17429+6920 copies/test) compared to OP swabs (37% and 2552+1965 copies/test) and NP swabs (16% and 651+501 copies/test) [122]. For 16 critically ill patients sputum and endotracheal aspirate samples all had detectable SARS-CoV-2 RNA at levels significantly higher than NP and OP swabs with positivity rates of 81% and 63% respectively [172]. In nine mild cases up to 5 dps, the maximum SARS-CoV-2 VL in sputum (2.35x10⁹ copies/mL) was higher compared to respiratory swabs (7.11x10⁸ copies/swab). However, examining paired sputum and swab samples 2-4 dps in seven patients showed higher virus concentration in swabs (two cases), sputum (two cases), and similar virus concentrations in both for the remaining five cases [131]. In a cohort of 52 patients, the positivity rates of sputum samples (77%) were higher than OP swabs (44%) with a significant difference when comparing cases with positive sputum sample and negative OP swab (40%) vs. those with negative sputum and positive OP swab (8%) [180].

Choosing the most appropriate respiratory specimen depends on timing in the infection course. However, well-documented studies comparing all respiratory and other sample types collected in a known timeline are limited. A preprint study in Guangdong on 866 respiratory samples from 213 symptomatic cases (37 severe), showed that apart from BAL, sputum is the most sensitive sample type for COVID-19 laboratory diagnosis, followed by NP swabs [26]. In the period 0-7 dps, the highest positivity rate was observed in sputum (severe cases 89%, mild cases 82%), followed by NP swabs (73%, 72%) and OP swabs (60%, 61%). In the period 8-14 dps the same order in positivity rates was observed: sputum (severe cases 83%, mild cases 74%), NP swabs (72%, 54%), and OP swabs (50%, 30%), as for [?] 15 dps: sputum (61%, 43%), NP swabs (50%, 55%), and OP swabs (37%, 11%). Sputum samples 0-7 dps also yielded the lowest median Ct values (25 in severe cases, 28.5 in mild cases). BAL samples 8-14 dps were positive for SARS-CoV-2 RNA in 12 severe cases and negative for three mild cases. Beyond 15 dps the study showed 79% positivity in BAL in severe cases [26]. Further peer-reviewed data was also in favour of sputum, or NP swabs [71, 77]. A retrospective study of 4880 cases in Wuhan found 38% positive rate for 4818 NP and OP swabs compared to 49% for 57 sputum specimens and 80% for 5 BAL [71]. Another Chinese study including 205 COVID-19 cases yielded overall 1070 samples with the following positivity rates: 93% for 15 BAL samples, 72% for 104 sputum specimens, 63% for 8 NP swabs, 46% for 13 fibrobronchoscope brush biopsy samples, 32% for 398 OP swabs, 29% for 153 feces samples, 1% for 107 blood samples [77]. Only BAL specimen sequencing, and BAL and sputum samples PCR could confirm SARS-CoV-2 co-infection with influenza A in an ICU patient, whereas repeated NP swabs were negative [78]. Although sputum might seem like a sample of choice, it was described that only a third of 1099 COVID-19 patients had a productive cough [50], suggesting that in practice NP swabs would be preferable in most cases. Higher sensitivity for NP swabs in comparison to OP swabs was observed as well in other studies and case reports [34, 52]. A study with sequential sampling in 18 patients (72 NP and 72 OP swabs) showed higher VL in the nose than the throat [34].

SARS-CoV-2 shedding potential in asymptomatic and pre-symptomatic individuals needs to be elucidated [74, 94, 101, 119, 139, 144, 155, 156, 160, 167, 170, 224, 227, 269, 270]. Multiple studies worldwide reported SARS-CoV-2 RNA detection in respiratory samples from cases with epidemiological link and no (189 adults, 29 children) [9, 31, 34, 36, 61, 70, 74, 94, 116, 119, 123, 139, 144, 155, 160, 199, 205, 214, 224, 227, 248] or mild/non-specific symptoms (23 adults, 1 child) [9, 12, 15, 18, 20, 24, 25, 28, 30, 39, 61, 74, 116, 227]. One described SARS-CoV-2 RNA detection in OP swabs for 17 days in an otherwise asymptomatic patient

[70]. In a series of testing campaigns in Iceland that led to SARS-CoV-2 RNA detection in NP+OP swabs of 1321 cases total, those reporting any symptoms ranged between 46% (random population screening) and 94% (targeted screening) [167]. At this stage, it is unclear whether SARS-CoV-2 affects the upper or the lower respiratory tract first, or maintains independent replication in both sites. Thus, choosing between NP and OP swabs, or sputum as sampling strategy should be done with the purpose (general population screening or confirmation of suspected cases) and potential infection timeline in mind. URT sampling would be preferable in the early infection days, especially in asymptomatic or mildly symptomatic suspected cases, whereas lower respiratory sampling provides more reliable confirmation in advanced COVID-19 with lungs involvement. Cases with an epidemiologic link, radiologic findings, and an initial negative result should be monitored further by PCR and evaluated in conjunction with their clinical presentation [10, 22, 35, 38, 41, 55, 56]. The discrepancy between URT and LRT test results has triggered a discussion about the lack of sensitivity of PCR testing. In a study among 1014 patients in Wuhan 59% (95%CI, 56%-62%) of OP swabs were positive whereas 88% (95%CI, 86%-90%) had chest CT findings within a median of one day, consistent with an earlier resolution of viral replication in URT than in LRT samples. Furthermore, 308 patients (75%) had negative PCR results in conjunction with radiologic findings and 14 out 15 cases with CT findings tested positive on a follow-up PCR within a mean of 5 days, a finding that may be more difficult to explain [41]. Another study that aggregated data on PCR results and CT imaging showed all 167 patients had a positive OP swab by the end of their hospitalisation [22]. A multicentre study of 80 COVID-19 cases (no critically ill) reported the following positivity rates in repeated OP and/or NP swabs collection until confirmation: 51%, 38%, and 11% upon the 1st-3rd test PCR test [56]. Another Hubei-based study reported SARS-CoV-2 RNA detection in OP swabs of 74%, 12% and 14% of 91 cases upon the 1st-3rd test and no significant difference between the 30 severe and 61 mild cases included [221]. A New York-based study on 5700 COVID-19 cases (incl. 1281 in ICU) reported detection upon 1st NP swab test in 97% (n=5517) of cases compared to 3% (n=183) with repeated tests [193].

Gastrointestinal shedding

Key points

- * SARS-CoV-2 isolation from feces and RNA detection regardless of gastrointestinal symptoms
- * Faecal sampling not recommended for diagnostic screening (unless laboratory diagnosis of suspected cases with negative respiratory tract results)
- * Prolonged gastrointestinal viral RNA detection up to seven weeks, well after respiratory tract clearance and symptoms resolution in some patients

We reviewed 47 studies providing data on gastrointestinal (GI) sampling in [?]629 COVID-19 patients, including stool specimens ([?]486 cases), anal/rectal swabs ([?]198), and others (endoscopic samples, n=14) (Supplementary Dataset) [9, 27, 39, 40, 42, 43, 48-51, 53, 58-60, 63, 64, 77, 84-86, 89, 91, 93, 100, 102, 105, 109, 117, 120, 121, 126, 131, 137, 152, 158, 168, 171, 172, 178, 179, 191, 203, 206, 229, 237, 240, 271].

SARS-CoV-2 was isolated from stool sample 15 dps from a COVID-19 patient with severe pneumonia (using Vero cells) [271] and from two patients without diarrhoea [77]. In a study involving nine mild cases, virus isolation (on Vero E6 cells) was unsuccessful in stool samples 6-12 dps from 4 patients, and no virus replication evidence was found through sgRNA assays despite detectable high VL [131]. SARS-CoV-2 nucleocapsid protein was detected in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cells in one patient [58]. The gastric fluid samples of six of 13 critically ill patients were positive for SARS-CoV-2 RNA [172].

GI disease has been described for some COVID-19 patients [9, 10, 12, 14, 16, 63, 83, 110, 272] and was one of the clinical signs associated with a positive SARS-CoV-2 test [272]. Though there was evidence of

SARS-CoV-2 RNA detection in the GI tract, it was not necessarily in cases with GI symptoms [48, 102]. Examining studies with an available timeline of sampling (Figure 1, Figure 2, Table, and Supplementary Table) SARS-CoV-2 RNA detection was reported between 3 and 50 dps in stool samples of 14 mild [59, 63, 120, 131] and 11 severe cases [58, 59, 172], regardless of the presence of diarrhoea. Anal swabs had detectable SARS-CoV-2 RNA between 3 and 45 dps in six mild [158, 171, 206] and seven severe cases [42, 172]. No systematic comparison between viral detection in stool and anal swabs was available.

Prolonged GI SARS-CoV-2 RNA detection after the resolution of respiratory symptoms and/or convalescence was observed in several studies [53, 58, 60, 102, 131, 137, 191], though infectious virus shedding is still an outstanding question. In a German study, stool samples remained RNA positive [?]21 dps for 6 mild cases, including a patient with potential independent intestinal tract replication, suggested by the authors by comparison with the SARS-CoV-2 URT kinetics [131]. Zheng and colleagues reported a 59% positivity rate in 842 stool samples from 96 patients and a median viral RNA detection duration of 22 (IQR 17-31) dps that was significantly longer than in sputum/saliva and serum samples [191]. In a study on 98 COVID-19 cases (18 severe), paired OP swabs and stool specimens for 74 cases yielded the following results: 41 with SARS-CoV-2 detection in stool for a mean 27.9 dps (SD 10.7) that was 11 days after the clearance in OP swabs with mean detection 16.7 dps (SD 6.7); while the remaining 33 patients with negative stool results had positive OP swabs for a mean 15.4 dps (SD 6.7). A patient had detectable SARS-CoV-2 RNA in stool 47 dps and another for 33 days after respiratory clearance. Disease severity was not associated with prolonged GI shedding in this cohort [102]. In another cohort of 42 patients (11 severe cases) with GI symptoms, 28 cases (nine severe) had a median RNA detection period of 11 (IQR 7-13) dps until first positive stool sample compared to 6.5 (IQR 3-7.25) dps for OP swabs. More than half (n=18, 5 severe) remained stool positive for median 7 (IQR 6-10) days after negative OP swabs [137]. A total of 39 (53%) of 73 hospitalized patients had detectable SARS-CoV-2 RNA in stool and for 17 patients (20%) it remained positive after respiratory samples turned negative [58]. Another Chinese study on recovering patients (n=55) found a median of 11 (9-16) dps until the first negative results in stool: 43 patients had a 2 (1-4) days median delay in clearance in feces compared to OP swabs, while in 12 patients both turned negative at the same time [53]. Sun and colleagues aggregated data on 165 stool samples and estimated a median/95th percentile time until loss of detection of 24.5/45.6 dps for 43 mild cases and 32.5/48.9 dps for six severe cases, both comparable to the estimates for NP swabs [240].

Like observations for stool specimens, prolonged SARS-CoV-2 RNA detection was reported for anal swabs [42, 70, 158, 168, 171, 172, 206]. Presence of SARS-CoV-2 RNA in anal swabs seemed linked to disease severity in a Guangzhou cohort (two severe and 16 mild cases) [9]. Zhang and colleagues found positive anal swabs in four of 16 patients upon hospitalization and six of 16 cases at day 5 [27]. A Chinese study with discharge criteria of two consecutive negative OP swab and a negative anal swab, reported a median RNA detection duration of 12 (IQR 9-14, range 4-34) days for 24 patients [158]. SARS-CoV-2 RNA detection in anal swabs [?]17 days was observed in an asymptomatic patient [70].

Large well-documented cohort studies are needed to estimate the proportion of COVID-19 cases with continuous GI shedding and the SARS-CoV-2 VL levels over time. A 29% SARS-CoV-2 RNA positivity rate in stool samples was observed in a study aggregating data on 205 patients (unclear how many provided the analysed 153 stool samples) [77]. Few studies (n=10) provided quantitative data on SARS-CoV-2 RNA detection in stool and anal swabs for 38 COVID-19 cases [27, 59, 63, 131, 158, 168, 171, 172, 206]. There was no significant difference between the VL in stool between 22 mild and 71 severe cases [191]. SARS-CoV-2 GI VL in adults seemed to be subjectively lower (higher Ct values) than in the respiratory tract in 25 cases [59, 63, 131, 168, 171, 172, 206], and higher (lower Ct values) in four mild cases [131, 168, 171], though meaningful conclusions cannot be drawn from such small sample sizes and non-systematic observations.

SARS-CoV-2 detection in blood

Key points

- * Blood sampling not recommended for initial diagnostics
- * No evidence of SARS-CoV-2 isolation from blood nor blood-borne transmission
- * SARS-CoV-2 RNA detection as a sign of severe disease up to 4 weeks post symptoms onset and use as a clinical monitoring tool

We reviewed 32 studies providing blood samples (whole blood, plasma or serum) data of [?]389 COVID-19 patients (Supplementary Dataset) [9, 10, 27, 39, 42, 48, 49, 51, 53, 58, 59, 63, 64, 77, 89, 105, 109, 118, 120, 122, 131, 133, 134, 145, 155, 172, 178, 182, 191, 196, 206, 223]. A systematic comparison of SARS-CoV-2 RNA detection in different types of blood samples was lacking. No virus isolation from blood samples was reported.

Summarizing data on COVID-19 patients with known infection timeline (Figure 1, Figure 2, Table, and Supplementary Table) SARS-CoV-2 RNA was detected 3-18 dps in 14 patients: 18 blood samples of ten severe cases [9, 42, 58, 59, 172] and 4 samples of four mild cases respectively [9, 39, 206]. SARS-CoV-2 RNA presence in blood was linked with disease severity [42] and reported in further 54 severe cases [10, 27, 105, 109, 120, 172, 182, 191]. Additionally, viral RNA was detected in blood samples from 35 mild cases [10, 27, 105, 109, 178, 191, 206], one asymptomatic infant [51] and 3 samples from unspecified cases [77]. SARS-CoV-2 RNA detection in blood might be useful as a laboratory sign of deterioration in severe cases. SARS-CoV-2 RNA was detected in blood samples from 16 mild cases for 10+6 days and seven ICU patients for 15+6 days [105]. A Chinese study reported a median viral RNA detection duration in the serum of 16 (IQR 11-21) dps, and 27% serum positivity rates in 22 mild cases compared to 45% in 74 severe cases. Detection rates peaked in weeks 2-3 since symptoms onset in all patients with detectable SARS-CoV-2 RNA (17 severe and 3 mild cases) and dropped to 11% (n=5) for severe cases and 0 for mild cases in week 4. However, VL had no significant difference between severe and mild cases [191]. A patient in critical condition had lower, but detectable SARS-CoV-2 RNA in plasma (Ct 35.8-38.4, 7-12 dps) compared to NP swabs (6.7-4.4 log10 copies/1000 cells, 7-24 dps) [120].

None of nine adults diagnosed with COVID-19 using OP swabs had detectable viral RNA in blood when tested with three different kits [48]. Although SARS-CoV-2 was detected and successfully isolated from respiratory samples, all 31 serum samples from nine mild cases tested negative [131]. Finally, none of the serum samples from 14 convalescent patients (no respiratory symptoms and two consecutive negative OP swabs) were positive for SARS-CoV-2 RNA despite simultaneous detection in OP swabs and stool [53].

Other specimens: oral fluid, tears, urine, cerebrospinal fluid, peritoneal fluid, semen

Key points

- * Oral fluid/saliva as a self-collectable alternative to respiratory sampling
- * SARS-CoV-2 RNA detection in oral fluid/saliva up to 4 weeks
- * Rare RNA detection and no SARS-CoV-2 isolation in conjunctival secretions
- * Limited SARS-CoV-2 RNA detection in urine and no virus isolation
- * SARS-CoV-2 visualisation in brain tissue and viral RNA detection in cerebrospinal fluid
- * SARS-CoV-2 RNA detection in semen

Fifteen studies reported on oral fluid sampling (with varying collection methods) in >339 COVID-19 cases [21, 62, 89, 97, 105, 109, 148, 164, 178, 190, 191, 194, 208, 209, 265]. No study compared the different collection methods, e.g. self-collection, sampling by a healthcare worker, swabbing, stimulated secretion. Self-collected deep throat (posterior oropharyngeal) saliva was suggested as an alternative to sputum and

yielded positive PCR results in 11 out 12 hospitalized COVID-19 patients in Hong Kong, as well as three positive and two negative virus cultures [21]. Further 23 patients with 173 saliva and endotracheal aspirate samples, studied by the same group, had median VL 5.2 log₁₀ copies/mL (IQR 4.1–7.0) at presentation. The highest saliva VL were reported in week 1 since symptoms onset (20 patients), followed by a gradual decline, and prolonged RNA detection [?]20 days (seven patients) [109]. In a summary of the first cases in Hong Kong viral loads in saliva were reported as 5.9x10⁶ copies/ml compared to 3.3x10⁶copies/ml in combined NP+OP swabs [62]. An Australian study screened 522 paired saliva and NP swabs and detected SARS-CoV-2 RNA in 33 saliva samples out of 39 cases confirmed by NP swab. Viral loads were lower in saliva compared to NP swab with both positive up to 21 dps. Among 50 subjects with negative NP swab, one had a positive saliva sample [190]. Similarly, a Thai study screened 200 participants with paired saliva and NP+OP swabs and found 16 cases with matched positive saliva and swabs, two with only saliva positive and three with only NP+OP swab positive. Viral loads were comparable and a 97.5% agreement was observed between saliva and combined NP+OP swabs [265]. A pre-print US study (later published in NEJM [273]) including 44 cases reported comparable/superior sensitivity of saliva to NP swabs and higher SARS-CoV-2 saliva VL for 38 matched samples [194]. In another pre-print study saliva was collected from 31 patients (26 mild, 5 severe cases) after stimulation of the salivary gland, paired with OP swab, and tested positive for SARS-CoV-2 RNA in four (3 severe, 1 mild) out of 13 cases with positive OP swab [97]. A study in Zhejiang confirmed COVID-19 in 96 patients by testing 668 sputum and 1178 saliva samples but did not specify samples types positivity rates separately. Taken together the latter declined from 95 to 54% in weeks 1-4 since symptoms onset with a median RNA detection duration of 18 (IQR 13-29) days [191]. In 25 cases SARS-CoV-2 RNA detection in the saliva was reported for 13+5 days in mild cases and 16.5+6 days in ICU patients [105]. A mild case in Wuhan had SARS-CoV-2 RNA detectable in OP swabs, saliva (Ct=18.7), and urine sediment 54 dps, and continuous detection in OP swabs over 70 dps [208]. SARS-CoV-2 was detected in all saliva samples collected by drooling technique from 25 severe cases [164], including two patients with same-day negative respiratory sampling in NP and bronchoalveolar swabs [164, 209]. A comparison between throat wash with saline solution and NP swabs collected 48-57 dps in 11 cases found inconsistent results and higher positivity rates in throat wash [148].

We reviewed six studies reporting conjunctival swab sampling in 137 COVID-19 cases [45, 105, 111, 120, 130, 172]. SARS-CoV-2 RNA was detected, but virus not isolated, in the tears and conjunctival secretions of one mildly symptomatic patient with conjunctivitis [45], while samples and cultures from 46 patients without ocular symptoms were negative [45, 111]. SARS-CoV-2 RNA detection in tears was also reported for one critically ill patient [172] and in 5 cases with unspecified disease severity [105]. Two severe cases out of 12 COVID-19 patients with ocular symptoms had positive conjunctival swabs [130]. No SARS-CoV-2 was detected in conjunctival swabs of 4 cases, incl. a severe one with conjunctivitis [120]

We reviewed 31 studies featuring urine samples from [?]369 patients [9, 39, 40, 43, 48, 49, 51, 53, 58, 59, 63, 64, 77, 89, 105, 109, 120, 122, 129, 131, 133, 137, 172, 178, 191, 197, 206, 208, 223, 237, 274]. None reported SARS-CoV-2 isolation from urine. A letter published shortly after the cut-off date of this review (not included in Supplementary dataset) described successful isolation of SARS-CoV-2 (on Vero E6 cells) at 12 dps in a severe case [275]. SARS-CoV-2 RNA was only detected in the urine of four patients (three patients with a positive sample upon OP swab turning negative) [53], at 7 dps in one woman with positive OP swab [206], in one critically ill patient with suspected systemic COVID-19 infection [172], in a case with urine abnormalities that later developed severe COVID-19 [274], and in a neonate with mild infection 6-17 dps [178]. Urine sediments were positive for SARS-CoV-2 RNA in five COVID-19 cases [129, 208]

Cerebrospinal fluid (CSF) sampling for a total of 14 patients was reported in eight studies [128, 138, 185, 189, 222, 230, 252, 257]. SARS-CoV-2 presence in the brain was evidenced post-mortem in a severe case: viral particles were observed in the frontal lobe and tissues samples, but not CSF, had detectable viral RNA [189]. SARS-CoV-2 RNA was detected (Ct>36 for N target only in a N/N2-based Japanese assay) in the CSF of a patient with meningitis 9 dps [138]. However, viral RNA was not detectable in CSF of six patients with Guillain-Barre syndrome [185, 252], nor of 2 patients with mild respiratory symptoms and suspected viral meningoencephalitis [230], nor of the two patients with intracranial haemorrhage and positive NP swabs

[222], nor of a child with Kawasaki disease [257]. CSF was not tested in a patient with suspected COVID-19 related acute necrotizing encephalopathy [128], nor in another two with Guillain-Barre syndrome [174, 244].

SARS-CoV-2 was not detected in peritoneal fluid samples collected during an appendectomy in a patient without respiratory symptoms, but positive NP swab [242].

We reviewed 5 studies reporting on semen testing in 102 COVID-19 cases [181, 197, 235, 267, 268]. SARS-CoV-2 RNA was detected in semen from six (four with acute COVID-19 and two recovering) out of 38 patients [235]. SARS-CoV-2 was not detected in semen collected during the recovery of 64 cases (9 convalescent severe, 54 mild, 1 asymptomatic) [181, 197, 267, 268], nor in the testis samples from a deceased severe case [181].

Pregnancy and infancy, vaginal sampling

We reviewed 30 studies including 400 pregnant women and their infants [19, 47, 54, 57, 64, 66, 81, 84, 92, 106, 110, 115, 118, 127, 146, 159, 162, 163, 173, 179, 201, 204, 210, 213, 223, 225, 226, 231, 234, 255]. No confirmed mother-to-child transmission was reported for these babies delivered mainly via Caesarean section. A single infant, delivered via C-section, isolated, and formula-fed, had a positive pharyngeal swab 36 hours after delivery. Cord blood and placenta tested negative, but it was uncertain whether it was a vertical transmission or nosocomial infection [84]. Similarly, another infant delivered via C-section and quarantined, had 5 NP swabs collected until 16 days of age negative for SARS-CoV-2 RNA, but serology suggestive of in utero infection. Amniotic fluid or placenta were not tested and vertical transmission could not be confirmed/excluded [115]. Buonsenso and colleagues reported on a single case of SARS-CoV-2 RNA detectable in placenta, umbilical cord blood and 3 of 5 breast milk samples collected in the first 5 days since delivery via Caesarean section. The infant was fed with expressed breast milk that tested negative on days 14-17 and his NP swabs were negative on days 1, 3, 18 as well as the OP and anal swabs on day 18 [225]. An infant and her mother were diagnosed with COVID-19 using NP swabs on day 7 post-delivery via C-section. The infant had negative NP swabs after 14 days and horizontal transmission was considered most likely [238]. Altogether SARS-CoV-2 RNA was not detected in 41 amniotic fluid [19, 54, 64, 92, 162, 179, 201, 223], nor in 41 umbilical cord blood [19, 54, 64, 84, 92, 162, 201, 225], nor in 10 placental tissue samples [54, 57, 64, 84, 92, 223, 225]. It is unclear whether SARS-CoV-2 could be transmitted through breastmilk, so far it was not detected in samples from 39 mothers [19, 51, 64, 84, 91, 92, 162, 178, 201, 225, 226, 237, 238].

It is unclear whether shedding occurs in the female reproductive systems posing risks for vaginal delivery and sexual intercourse. In a study of 35 mild cases with age range 37-88 years, viral RNA was not detected in exfoliated cervical cells nor vaginal fluid [226]. Vaginal fluid and vaginal swabs in further 22 women also tested negative [92, 115, 133, 179, 201, 223, 237] incl. 10 severe cases [133].

Children and adolescents

We reviewed 64 studies describing COVID-19 in 1510 children and adolescents [9, 17, 31, 32, 45, 49, 51, 56, 68, 74, 83, 84, 86, 87, 89, 91, 93-95, 100, 101, 106, 108, 112, 114, 115, 121, 126, 140, 143-145, 155, 156, 160, 166, 168, 177, 178, 183, 184, 193, 199, 203, 205, 212, 214, 225, 227, 229, 232, 233, 236-238, 243, 246, 247, 249-251, 253, 257, 264]. Some further studies included cases <18 years old grouped with adults and/or provided incomplete stratification by age (marked as NA in Children No column of Supplementary dataset). In a study of 36 mild cases with ages 1-16 years it took in mean 10 (range 7-22) days until first negative results in NP swabs [114]. An asymptomatic 6-month infant maintained detectable SARS-CoV-2 RNA in NP swabs until 17 days of hospitalization and had a positive stool sample on day 9 [51]. In an Italian study on 168 paediatric cases (4 asymptomatic, 131 mild, 33 severe) nationwide diagnosed via NP/OP swabs 67% had at least 1 parent testing positive [233]. Verdoni and colleagues reported an increase of Kawasaki-like disease cases in March-April 2020 with two of ten children with positive NP swabs and eight with positive serology [257]. A case-report documented an episode of detectable SARS-CoV-2 RNA in blood and transient

fever in an otherwise asymptomatic 6-month infant [51]. Prolonged GI SARS-CoV-2 RNA detection after respiratory samples clearance was observed in stool samples up to 35 dps for 20 children aged 0.15-10 years [49, 89, 91, 100, 121, 126, 237] and in rectal swabs [?]3 weeks in 15 cases aged 0.15-17 years [86, 91, 93, 168, 203]. In a cohort of 46 children and adolescents, four had positive rectal swabs within 2-12 days after recovery and discharge with negative OP swabs [229]. An asymptomatic girl had SARS-CoV-2 RNA detectable in anal swabs for 42 days, but not in NP swabs [203].

Higher SARS-CoV-2 VL in stool than OP swabs were reported for >20 days in an infant with mild COVID-19 [121]. Eight children had higher average VL in anal swabs compared to NP swabs [86]. Han and colleagues reported of a neonate with mild COVID-19 who had SARS-CoV-2 RNA detectable in respiratory swabs (NP swab VL 1.2x10¹⁰ copies/ml and OP swab VL 1.3x10⁸ copies/ml to undetectable 4-17 dps), stool (VL 1.7x10⁶ copies/ml to 4.1x10⁷ copies/ml 6-18 dps), saliva (6-9 dps), plasma (5-10 dps) and urine (6-17 dps) [178].

Immunocompromised individuals

We reviewed 32 studies including 317 immunocompromised individuals [16, 50, 80, 88, 95, 96, 103, 110, 136, 147, 151, 152, 154, 155, 165, 169, 188, 191, 193, 207, 218, 219, 221, 233, 245, 249, 251, 253, 257-261], however specifics for them were rarely outlined in cohorts. Data on SARS-CoV-2 shedding patterns in immunocompromised individuals are still limited and quantitative data are lacking. SARS-CoV-2 RNA was detected in NP swabs 57 and 63 dps in a kidney transplant recipient following clinical recovery and hospital discharge 35 dps [258]. In a report on two lung transplant recipients, an asymptomatic adolescent had a positive NP swab 26 days after diagnosis, while a mildly symptomatic adult's NP swab was negative for SARS-CoV-2 RNA after 2 weeks [251]. In a study of 90 transplant recipients with COVID-19, seven (three mild, four severe) cases had an initial negative NP swab, but dps were not reported [207]. Evidence of endothelial cell infection and endothelitis was observed in three severe COVID-19 cases, incl. a renal transplant recipient [188].

A person living with HIV (PLHIV) and HCV had pneumonia resolution and negative NP swabs 10 dps but delayed antibody response 42 dps [152]. Further three PLHIV had a similar mild course with negative NP and OP swabs after 1 week [218] and another two PLHIV after 2 weeks from diagnosis [80, 165].

Discussion and knowledge gaps

Sensitive molecular diagnostics through PCR and correct sampling and test interpretation are crucial for accurate COVID-19 diagnosis and thereby essential for good clinical practice. Furthermore, they are a key factor in outbreak phases where active case finding in combination with quarantine and contact tracing are crucial for outbreak control. We reviewed current knowledge on the kinetics of SARS-CoV-2 RNA shedding in different clinical samples of 32515 COVID-19 patients to inform clinical and public health decision making.

Our review comes with limitations like the choice of rapid instead of systematic style. Given the need for timely diagnostics information in the current pandemic and the overwhelming amount of publications indexed daily, we opted for a faster adapted systematic approach. We did not access the included publications for biases nor could fully trace for duplicate reporting of cases. Full comparability of the assays used could not be assured due to the lack of standardized diagnostic set-up across the world with respect to e.g. sampling materials, transport conditions, cell culture, extraction and PCR platforms. These were infrequently detailed in the publications. Furthermore, we did not review separately results from PCR assays targeting different parts of SARS-CoV-2 genome, for example E [10, 276, 277], RdRp [9, 276, 277], ORF1ab [11, 50, 51, 59, 276], ORF1a [276], ORF1b [276, 278], N [11, 50, 51, 59, 276, 278, 279] or S [9, 51, 59, 276, 280, 281] genes, though we tried to provide the authors' estimations of viral loads or if not Ct values, where available. However, relatively few of the reviewed articles provided such detailed data, and we could not assess the

data quality. We could not estimate to what extent the genetic drift in the SARS-CoV-2 genome affects the reported PCR results, nor could summarise false-positive or false-negative rates [282] due to insufficient data. Regular monitoring of the assays performance, detailed reporting and strict quality assurance mechanisms in accredited laboratories are vital to molecular diagnostics of SARS-CoV-2.

Respiratory tract specimens are the samples of choice for wide-spread screening and clinical course monitoring purposes, as well as for discharge and de-isolation [283, 284]. Further reports with well-documented sampling time points, comparing the different types of respiratory samples and their diagnostic window of use, are needed. Viral RNA concentrations in the URT peak in the early infection days, including in asymptomatic and mildly symptomatic cases. SARS-CoV-2 was successfully isolated from respiratory samples with data suggesting independent replication potential in both the upper and lower respiratory tract. Thus, respiratory sampling is the optimal strategy for both symptomatic and pre-/a-symptomatic cases and for the latter should be examined in conjunction with epidemiological evidence and clinical follow-up.

Although molecular detection on upper respiratory tract samples is the recommended method to diagnose a SARS-CoV-2 infection, serology is occasionally imperative to complement RT-PCR findings, e.g. in cases of insufficient clinical sensitivity of the RT-PCR over the disease course period [285]. In addition, serology can aid decision making on clinical and infection prevention management, e.g. by confirming the presence of SARS-CoV-2 specific (neutralizing) antibodies in cases with consistently low viral loads (high Ct values) in upper respiratory samples [286, 287]. SARS-CoV-2 RNA detection in the respiratory tract during convalescence can be prolonged. However, detection of viral genomes does not directly imply the presence of infectious virus and thereby infectivity. More information on the presence of viable SARS-CoV-2 infectivity is urgently needed, especially with de-isolation strategies in mind.

Although faecal-oral transmission has not been confirmed, it cannot be firmly excluded due to evidence of SARS-CoV-2 isolation from the GI tract [58, 271]. The detection of viable SARS-CoV-2 in faecal samples also has implications for the diagnostic possibilities of faeces tests. Laboratory diagnostic and safety protocols might need adjustments, for example by implementing inactivation steps and flow cabinet work. Stool and anal swabs are not samples of choice for screening purposes, though they might play a role in clinical monitoring. Some data suggested a shift from respiratory to GI shedding in the course of COVID-19 infection or independent replication in the GI tract. More information is needed on the significance of SARS-CoV-2 detection in faecal samples and how it relates to the timing of convalescence, as well as to the viral shedding specifics in children.

SARS-CoV-2 RNAemia has been detected mainly in severe cases and blood sampling could be useful in monitoring hospitalized patients. At this stage, there is no evidence to suggest SARS-CoV-2 could be transmitted through blood. More systematic data are needed to guide blood and organ transplantation safety protocols [288].

So far vertical transmission of SARS-CoV-2 seems unlikely or extremely rare with single reports on viral RNA detection in samples obtained during delivery. More studies on this route as well as potential transmission via sexual intercourse are needed. Viral RNA was detected in semen [235], but virus isolation was not attempted, and sexual transmission potential remains an open question. Data on SARS-CoV-2 kinetics in vulnerable groups like immunocompromised patients are insufficient. Neurological signs and syndromes associated with COVID-19 and the diagnostic/monitoring potential of CSF testing remain to be clarified.

In conclusion, using SARS-CoV-2 molecular testing by amplification techniques to the maximum of its potential is a combination of choosing the most appropriate sample type, collected with adequate sampling technique, and with the infection timeline in mind. Like all diagnostic techniques, it should be analysed considering strengths and limitations, and in conjunction with the clinical presentation and epidemiological evidence. Further well-documented systematic studies are needed to characterise fully the COVID-19 clinical course and guide public health decisions concerning optimal testing strategies.

Conflict of interest

None declared

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Authors' contributions

CBEMR, LMK and KRS conceived the study design. KRS searched, compiled, and organised the information, and wrote the manuscript drafts. CBEMR, LMK, AAE, AM and MPKG reviewed the evidence and agreed on the conclusions. KRS and CBEMR finalised the manuscript text. All authors reviewed and contributed to the final manuscript.

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