Clinical Virology of SARS-CoV-2

Audience: PHE internal /SAGE review
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Aim

To review current understanding of the kinetics of viral shedding from humans infected with SARS-CoV-2. Note, SARS-CoV-2 was previously known as 2019-nCoV and WN-CoV.

To put this into context, we also report on what is known about viral shedding from cases of SARS-CoV and MERS-CoV. These are human coronaviruses with ~80% and ~50% genetic identity to SARS-CoV-2, respectively[1].

SARS-CoV

The incubation period for SARS is typically 2-7 days (mean 4.6 days). 95% of patients developed symptoms within 12.5 days of infection[2].

Infectiousness of SARS-CoV is generally believed to coincide with, but not precede, clinical symptoms. There have been reports of small numbers asymptomatic/pauci-symptomatic infections with SARS-CoV.

SARS-CoV excretion is relatively low during the initial phase of illness. The progression to disease severity in SARS is accompanied by increase in viral shedding in several body compartments. Viral load increases in respiratory samples in the second week of SARS illness[3]. Viral load is greatest in samples taken from the lower respiratory tract (LRT), peaking at around day 10. SARS-CoV RNA was detected in only 32% of individuals in nasopharyngeal aspirates at initial presentation (mean 3.2 days after illness onset) but in 68% at day 14 and in over 90% of faecal samples collection in the 2nd week of illness, peaking around day 15-17[4].

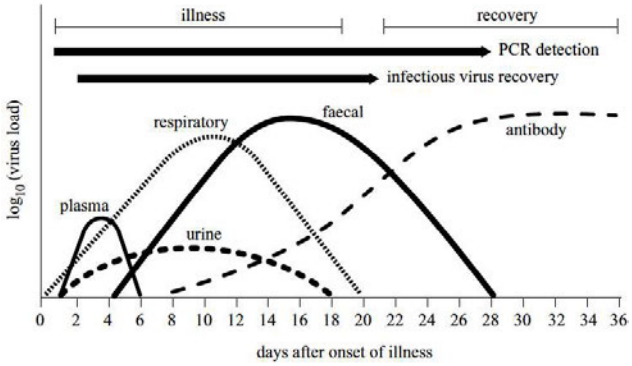


Figure 1. Schematic diagram of the course of virus shedding and detection in body fluids during SARS illness and recovery. Onset of illness is taken to be the onset of symptomatic fever. Taken from Bermingham *et al* [4] (HPA/PHE data).

MERS-CoV

Clinical features of MERS range from asymptomatic/mild disease to ARDS and multiorgan failure resulting in death, especially in individuals with underlying comorbidities[5]. Data on viral shedding from MERS patients is more limited than for SARS-CoV.

Similar to findings in SARS-CoV cases, viral loads have frequently been reported to be higher in LRT than upper respiratory tract (URT) samples[6–10]. Shedding from the URT can be detected between days 1-14, peaking around day 5-7. From the LRT, viral shedding can continue for longer and peaks in weeks 2-3[10–12]. Average and peak LRT viral loads in MERS are similar to those in SARS[7].

Overall, viral loads detected in non-respiratory samples from MERS patients are significantly lower[7]. However, a lack of data limits accurate characterisation. Viral RNA in blood has been detected in the first and second weeks of MERS illness, but in severe cases can be further prolonged[7,10,11,13]. Live virus isolation from serum samples was not successful[7].

Compared to SARS-CoV, viral shedding from stool has been reported far less frequently for MERS-CoV and is associated with low viral loads (high CT values)[7,9,14]. Where attempted, live virus was not successfully isolated from stool samples of MERS cases[7,11]. Infrequent reports of low quantities of MERS RNA detected in urine have been associated with severe disease[7,9,11] and no live virus could be isolated from urine[11].

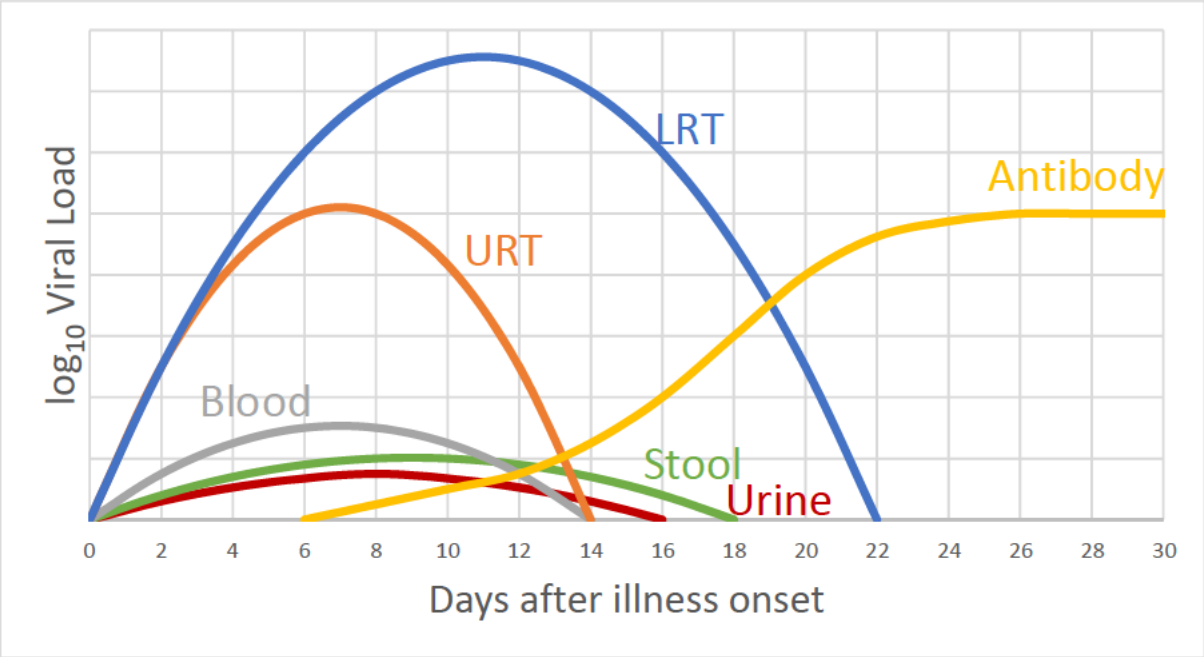
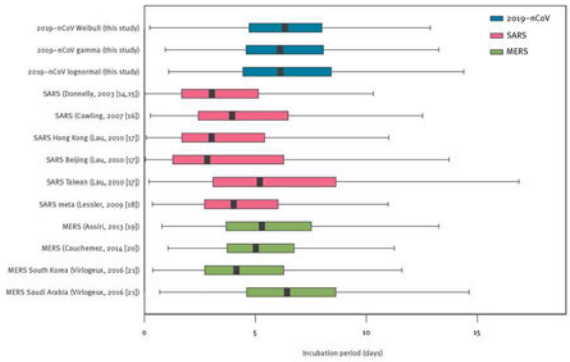


Figure 2. Schematic diagram of the course of virus shedding and detection in body fluids during MERS illness and recovery. Data represents an estimation only and is derived from the limited published literature available.

SARS-CoV-2

Current estimates of the incubation period of SARS-CoV-2 range from 2-11 days with a median of 6.4 days[15].

A



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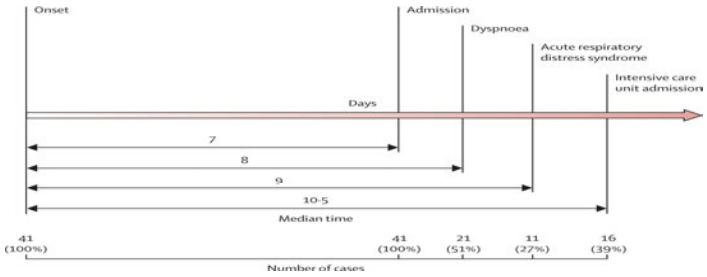


Figure 3. (A) Incubation periods of SARS, MERS and SARS-CoV-2 (Backer *et al*, Eurosurveillance[15]). (B) Timeline of SARS-CoV-2 illness (Huang *et al*, Lancet[16]).

SARS-CoV-2 uses the same ACE2 receptor as the highly pathogenic SARS-CoV virus[17]. The endemic human coronavirus HCoV-NL63, which predominantly causes mild-to-moderate disease, also uses the ACE2 receptor. HCoV-NL63 can cause a more severe clinical presentation in young children, the elderly and the immunocompromised[18]. This indicates a diversity of pathogenesis associated with receptor preference. Data shown in Figure 3A&B indicate several similarities in the trajectory of the development of severe illness in SARS-CoV-2 compared to SARS-CoV, supporting an assumption that peak virus shedding might be seen later during the course of illness in cases where progression to severity occurs. However, there have also been several reports of asymptomatic/pauci-symptomatic infection with SARS-CoV-2, more so than with SARS-CoV (WHO daily SitReps).

To date, there are no studies reporting detailed data on sequential sampling from SARS-CoV-2 infected persons. This includes information shared at the WHO meeting in the week of 10th February 2020.

A case of mild illness from [redacted] reported initial SARS-CoV-2 detection on day 4 of illness with more viral RNA found in nasopharyngeal (NP) specimens than oropharyngeal (OP) specimens (CT values 18-20 versus 21-22). Both URT specimens obtained on illness day 7 remained positive for SARS-CoV-2, including persistent high levels in the NP swab specimen (Ct values, 23 to 24). By day 11, NP and OP specimens showed a trend toward

decreasing levels of virus and on day 12 the OP specimen was negative. Stool obtained on illness day 7 was also positive for SARS-CoV-2 (Ct values, 36 to 38). Serum specimens were negative for SARS-CoV-2.

Viral RNA has been detected in blood of patients with severe SARS-CoV-2 disease. In the report by Huang *et al.*[16], viral RNA was detected in plasma samples from 6 of 41 (15%) patients, but the timing of samples related to illness onset was not stated.

In a recent study, self-collected saliva was found to be positive in 11/12 patients with SARS-CoV-2, with 3 samples subsequently yielding infectious virus[19].

UK data on SARS-CoV-2

The utility of sequential sampling to inform understanding of viral shedding and disease phenotype, and the potential for detection of virus in non-respiratory samples, has been recognised from the outset of the PHE response to this episode. Advice on SARS-CoV-2 sample set has taken this into consideration (Appendix 1).

Data available from UK cases is shown in Appendix 2 and summarised below.

The majority of UK cases have been identified several days after illness onset. Some of these have been detected after 10 days of illness, which is likely to be towards the end of disease. This has therefore offered limited opportunity for serial sampling early after illness onset, which may be the most informative.

Nine cases of SARS-CoV-2 have been detected in the UK so far. One remains under investigation and is not discussed. Of these, eight are fully confirmed (one had extremely low viral load but was epidemiologically linked to a cluster). Seven out of eight had suitable material for virus isolation. Three out of seven UK cases yielded a virus isolate, indicative of the presence of infectious virus; these samples had CT values <30.

All cases have been identified through detection of SARS-CoV-2 in upper respiratory tract samples. Lower respiratory tract material has only been available in very few cases, which is relevant to consideration of disease phenotype. Stool has been positive in two cases. No blood samples have demonstrated the presence of SARS-CoV-2 RNA, suggesting that if viraemia exists it is early and low.

Conclusions

In SARS-CoV and MERS-CoV, LRT samples are generally found to have higher viral load than URT samples and the peak of shedding from severe cases appears to occur around the second week of illness. Faecal samples were more frequently positive and with higher viral load in SARS-CoV than MERS-CoV.

Data on SARS-CoV-2 is currently limited but suggests that nose and throat swabs are reasonable samples to use. Faecal shedding does occur, and so far there is no/limited evidence for viraemia, though this may reflect lack of early sampling.

This is interim report that will be updated as more information becomes available.

Appendix 1

SARS-Co-V-2

Serial sampling and discharge criteria

PHE & Airborne HCID network

Scope

This interim guidance applies to hospitalised patients with confirmed SARS-CoV-2 infection and is intended for HCID treatment centres only; should arrangements for managing hospitalised confirmed patients change in the future, the guidance will be reviewed and updated.

For discharge planning purposes at HCID treatment centres, negative respiratory samples are an absolute requirement (see below); it is expected that testing of other sample types and interpretation of results will be discussed with PHE Colindale on a case-by-case basis. Again, this case-by-case arrangement will be kept under review by the Airborne HCID Network and PHE.

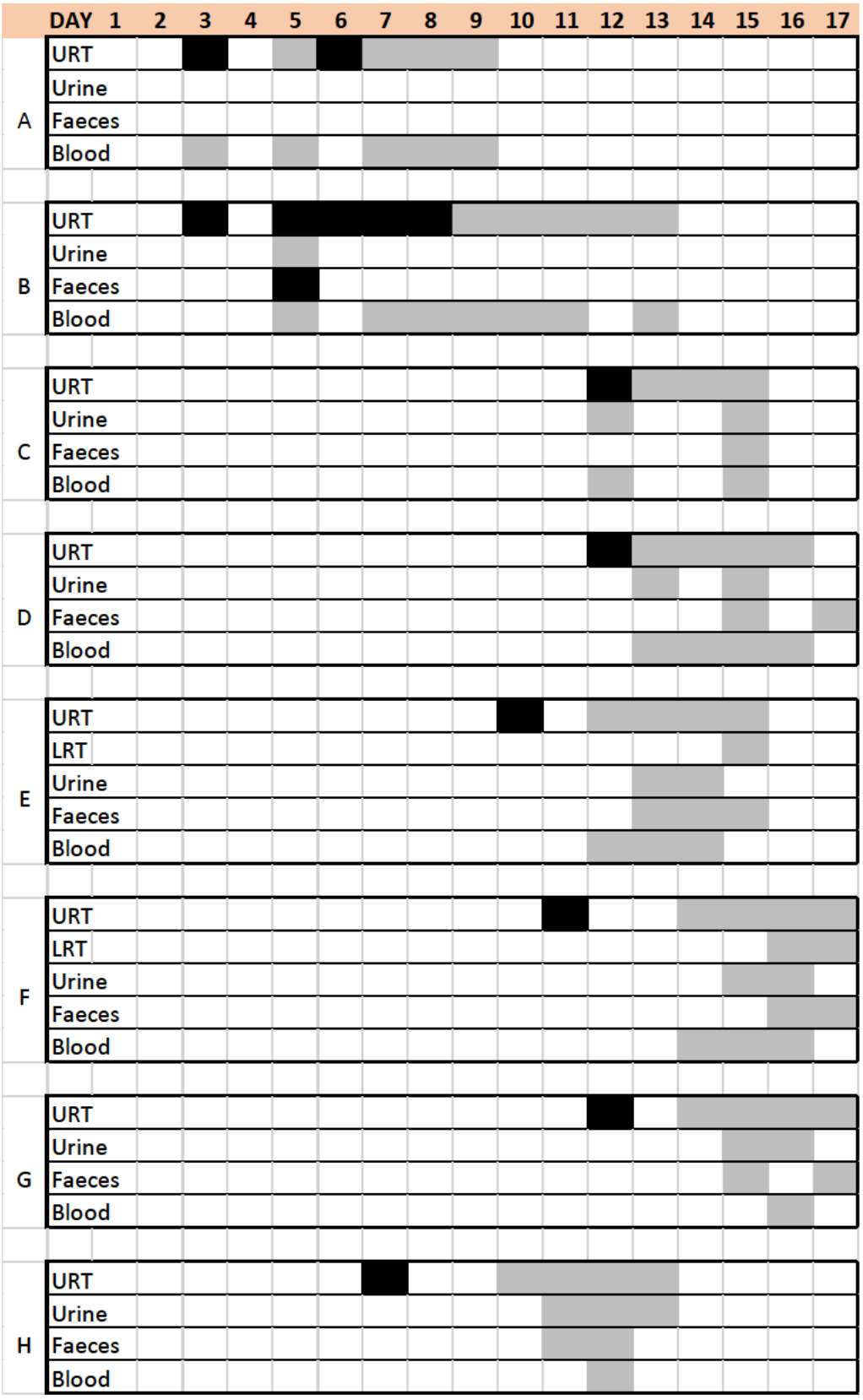
1. Once you have confirmed a case, **take a full sample set as follows:** Upper and lower respiratory tract samples (if lower are available), EDTA blood, serum, faeces and urine.

2. **Continue to take this sample set daily** for the duration of the acute medical illness, and then until each sample type is shown to be negative twice. Once a sample type is negative twice, 24 hours apart, there is no need to continue to test that sample site. If new signs and symptoms develop subsequently while hospitalised, consider testing the relevant sample type again (eg faeces if new onset diarrhoea).

3. **These results will inform the following discharge assessment:**
    1. A clinical assessment has determined that the patient has recovered from their acute illness, to a sufficient extent that they no longer require hospitalisation for medical reasons
    2. Two respiratory samples obtained 24h apart are negative for SARS-CoV-2 RNA. This applies to upper respiratory tract and lower respiratory samples i.e. if both upper and lower respiratory tract samples were positive previously, both sample types must be shown to be negative subsequently, on two occasions 24 hour apart. If a lower respiratory tract sample can no longer be obtained (e.g. stopped producing sputum), then negative upper respiratory tract samples are sufficient.
    3. If SARS-CoV-2 RNA has been detected in other sample types, such as blood, urine or faeces, these should also be negative on two occasions 24 hours apart. In some cases, a risk assessment may support discharge despite SARS-CoV-2 being detectable in a sample type (such as urine or faeces), as long as appropriate infection prevention and control measures can be instigated and maintained.

Appendix 2

	POS
	NEG



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