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REVIEW ARTICLE

Severe acute respiratory syndrome coronavirus-2: implications for blood safety and sufficiency

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Background and Objective Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus, first identified in China at the end of 2019 and has now caused a worldwide pandemic. In this review, we provide an overview of the implications of SARS-CoV-2 for blood safety and sufficiency.

Material and Method We searched the PubMed database, the preprint sites bioRxiv and medRxiv, the websites of the World Health Organization, European Centre for Disease Prevention and Control, the US Communicable Diseases Center and monitored ProMed updates.

Results An estimated 15%–46% of SARS-CoV-2 infections are asymptomatic. The reported mean incubation period is 3 to 7 days with a range of 1–14 days. The blood phase of SARS-CoV-2 appears to be brief and low level, with RNAaemia detectable in only a small proportion of patients, typically associated with more severe disease and not demonstrated to be infectious virus. An asymptomatic blood phase has not been demonstrated. Given these characteristics of SARS-CoV-2 infection and the absence of reported transfusion transmission (TT), the TT risk is currently theoretical. To mitigate any potential TT risk, but more importantly to prevent respiratory transmission in donor centres, blood centres can implement donor deferral policies based on travel, disease status or potential risk of exposure.

Conclusion The TT risk of SARS-CoV-2 appears to be low. The biggest risk to blood services in the current COVID-19 pandemic is to maintain the sufficiency of the blood supply while minimizing respiratory transmission of SARS-CoV-19 to donors and staff while donating blood.

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Introduction

On 31 December 2019, China notified WHO of a cluster of pneumonia cases with unknown aetiology in the city of Wuhan, Hubei Province [1]. By 7 January 2020, Chinese scientists had identified the pathogen as a novel coronavirus [2,3]. Initially referred to as 2019 novel coronavirus (2019-nCoV), the virus has now been designated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), classified within the *Severe acute respiratory syndrome-related coronavirus* species, *Sarbecovirus* subgenus, *Betacoronavirus* genus and *Coronaviridae* family [4–6]. Sequence analysis has indicated that SARS-CoV-2 is closely related to SARS-CoV (approximately 80% sequence homology) [5,7,8]. The disease associated with SARS-CoV-2 has been designated as coronavirus virus disease 2019 (COVID-19) [9].

On 30 January, the WHO Emergency Committee declared the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) [10] and on 11 March, declared it a pandemic [11]. As at 17 September 2020, WHO had reported over 29.4 million confirmed

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COVID-19 cases globally [12]. Initially, the highest number of confirmed COVID-19 cases was reported in China. However, by mid-March, the highest number of new confirmed cases was being reported in the European Region (particularly Spain, Italy, France, Germany, the UK and, subsequently, the Russian Federation); since mid-May, the highest number of new cases has been reported in the Region of the Americas, primarily due to the US and Brazil, and the South-East Asian Region, primarily due to India [12].

In this review, we summarize what is currently known about SARS-CoV-2 and the associated disease, COVID-19, particularly those characteristics of the virus that are relevant to assessing the potential risk to blood safety. We then discuss whether the virus is potentially transfusion-transmissible and consider the impact of risk mitigation strategies that can be employed by blood centres. Additional supporting references are included in the supplementary material file.

Epidemiology of SARS-CoV-2

The origin of SARS-CoV-2 and mode of transmission to humans has not been definitively established [13–15]. Sequence homology studies indicate that SARS-CoV-2 may have originated from a bat coronavirus and transmitted to humans via an intermediate host [7,14,16,17].

Many of the earliest, although not all, reported cases of SARS-CoV-2 (prior to 1 January 2020) were directly or indirectly associated with a seafood/animal market in Wuhan, which now appears to have been due to human-to-human transmission [18,19]. Subsequently, the rapid geographical spread and increase in case numbers of SARS-CoV-2 in China and beyond has demonstrated that sustained person-to-person transmission is now the primary mode of transmission [3,20]. COVID-19 cases have been reported in clusters typified by people coming into close contact in confined spaces, often with the identification of superspreaders [21–23]. These include households, public gatherings, conferences, healthcare facilities, religious gatherings and cruise ships [3,24–26]. For example, the Diamond Princess cruise ship off Japan resulted in 712 confirmed cases [12] and there were 600 confirmed cases on the Ruby Princess in Sydney, Australia [27].

Evidence indicates that the predominant mode of human-to-human SARS-CoV-2 transmission is via airborne droplets. SARS-CoV-2 has been demonstrated to infect cells of the upper respiratory tract and isolated from a variety of human respiratory fluids including saliva, bronchoalveolar lavage fluid, nasopharyngeal and throat swabs [28–30]. Transmission by aerosol particles is not a major mode of transmission [31–33]. *Under laboratory conditions*, it has been demonstrated that infectious virus is stable for a limited time on surfaces (fomites) and in generated aerosols contaminated with cultured virus. [34,35]. Studies of isolated COVID-19 patients and hospital wards have reported natural SARS-CoV-2 RNA contamination of commonly used items, surfaces, outdoor environment and air samples, suggesting the contamination of surfaces by airborne droplets [33,36–38]. However, these studies either did not detect or did not test for infectious virus and therefore the importance of fomites in the transmission of SARS-CoV-2 is not clear.

There is evidence that SARS-CoV-2 is transmissible by infected asymptomatic and pre-symptomatic individuals [39,40]. A number of transmission clusters with evidence of possible transmission from pre-symptomatic individuals in close contact have been reported [41–44]. Several studies have reported serial intervals (time from symptom onset in a primary case to symptom onset in a secondary case) shorter than the incubation period, suggesting asymptomatic and pre-symptomatic transmission [45,46]. In addition, SARS-CoV-2 RNA has been detected in respiratory swabs and faeces from asymptomatic individuals [47,48].

There is currently no evidence for intrauterine transmission of SARS-CoV-2 [49,50] or vertical transmission to newborns [51]. A small number of cases of SARS-CoV-2 RNA detection in the breast milk of infected nursing mothers have been reported [52–54]. However, the detection of infectious virus in breastmilk or transmission by breastfeeding has not been reported, consistent with MERS-CoV and SARS-CoV. There is no evidence of sexual transmission of SARS-CoV-2 [51,55]. One study has reported evidence that SARS-CoV-2 may be transmissible by the ocular conjunctival route under some circumstances, however this has been questioned [56–58]. SARS-CoV-2 has been shown to infect cells in the ileum and colon, and infectious virus has been isolated from rectal swabs and stool, indicating that the digestive system may also be a route of infection and faecal transmission may be possible [59–62].

COVID-19: disease characteristics

Directly estimating the proportion of asymptomatic SARS-CoV-2 infections in the general population is not currently possible as the total number of infections is unknown, and awaits the publication of reliable seroprevalence studies. In addition, reported estimates of the proportion of asymptomatic infections vary due to the differences in methodology and the epidemiology of the study population. Three studies have reported estimates based on specific study groups in which all individual

were tested for SARS-CoV-2 RNA (but not serologically) [63–65]. The estimated percentage of asymptomatic infections varied between a mean of 30·8% (95% CI: 7·7–53·8%) and a median of 34·6% (95% credible interval: 29·4%–39·8%). Subsequently, there have been a number of additional studies and meta-analyses, with estimates varying from 15% (95% CI: 12–18%) to 46% (95% CI: 18–73%) [66–69].

The incubation period for SARS-CoV-2 infection has been modelled by several studies, most showing close agreement with the estimated means/medians ranging from 3·0 days (IQR: 2·0–6·0) to 7·5 days (95% CI: 4·1–10·9) [70–72]. There was some variation between studies for the estimated ranges of the incubation period but most were within the range of 2 to 11 days and almost all infections developed symptoms by day 14. These estimates have been supported by several subsequent meta-analyses which estimated mean values between 4·24 days (95% CI: 3·03–5·44) and 6·93 days (95% CI: 6·11–7·75) [68,73–75].

Studies from several countries have demonstrated that the majority of reported confirmed COVID-19 cases in the general population are mild/moderate [76–79]. For example, a large study of reported confirmed cases in China (n = 44 672) reported that 81% of cases were mild infections, 14% were severe, 5% were critical and 2·3% of cases died [3,20]. The median age of COVID-19 patients varies between countries due to differences in epidemiology and the stage of the pandemic. In initial reports, based primarily on Chinese studies, the median age of patients varied between 47 and 56 years and a majority were males (53·4–73%) [18,80]. Subsequently, studies from several countries have reported the mean age of COVID-19 patients, varying from 39 years (Brazil) to 72 years (US) [77,81–84]. For most countries, the average age of patients was >60 years. Although there is some variation between studies, typically the most common symptoms were fever (83–98%), cough (59–81%), myalgia/fatigue (44–70%) and breathing difficulties (31–55%). Less common symptoms included confusion, headache, sore throat, rhinorrhoea, congestion, expectoration, cutaneous symptoms (including chilblain-like lesions), cardiovascular complications, gastrointestinal symptoms (diarrhoea, anorexia, nausea and vomiting) and neurological symptoms. People of older age, male gender, smokers or those with underlying disease, particularly cardiovascular disease, chronic respiratory disease, hypertension, diabetes, chronic kidney disease and Down's syndrome, are at a higher risk of developing severe symptoms [3,20,77,83–88]. Patients with severe disease may also have neurologic symptoms including acute cerebrovascular diseases, impaired consciousness, seizures, meningoencephalitis, Guillain–Barré syndrome and skeletal muscle injury [89,90]. More recently, acute temporary loss or impaired taste, olfactory and chemesthesis function have been recognized as common (>60% in some studies) and specific early symptoms of SARS-CoV-2 infection [91–93]. Compared to adults, it appears children have a higher proportion of asymptomatic infections, milder symptomatic infections, a lower fatality rate and possibly a longer incubation period [94–96]. A syndrome, which has Kawasaki disease-like symptoms and referred to as multisystem inflammatory syndrome in children (MIS-C) or paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-1 (PIMS-TS), has been reported in children with COVID-19. The syndrome has a wide range of presenting symptoms, from fever, inflammation and gastrointestinal symptoms to myocardial injury, shock and development of coronary artery aneurysms [97–100].

While the fatality rate among reported confirmed cases varies substantially between regions, the risk factors for death are consistent, namely older age, male gender and comorbidities [101–103]. The Chinese study noted above reported no fatalities in patients under 10 and 0·2% fatality rate in those between 20 and 40, but increasing to 8·0% for those 60–69 and 14·8% for those 80 or over [20,102], and similar findings have been reported by other studies [102–107]. The same Chinese study found that male patients were overall approximately 1·6 times as likely to die than female patients (2·8% vs. 1·7%), a finding also reported by other studies [102,105]. Compared to all reported COVID-19 cases, patients with a fatal outcome have higher rates of comorbidities including hypertension, diabetes, chronic vascular disease and chronic lung disease [102,104,105]. It is currently not possible to accurately estimate the total number of SARS-CoV-2 infections due to asymptomatic infections which would typically not be reported nor diagnosed, underreporting of symptomatic cases and lack of attribution of COVID-19 as cause of death [108–110]. As a consequence, it is not possible at present to estimate the infection fatality rate (IFR) for all infections (reported and unreported). However, a number of studies and meta-analyses have modelled the IFR, taking into account the proportion of unreported infections. While estimates of the mean overall IFR vary from 0% to approximately 5%, most studies reported values between 0·2% and 2% [68,111–114].

Data on SARS-CoV-2 RNA detection in blood (RNAaemia) are limited, and the blood phase of SARS-CoV-2 infection has not been well defined. A number of studies have shown that only a small proportion of COVID-19 patients had detectable RNAaemia, although most had detectable viral RNA in respiratory swabs [18,59,115–120]. The RNAaemia period appears to be brief, low level and typically associated with more severe disease

symptoms. There has been one report demonstrating that SARS-CoV-2 RNA detected in the blood of patients was not associated with infectious virus [121]. A single case study of a patient with an extended period (approximately 40 days post-symptom onset) of RNAaemia has been reported [122]. However, the RNA levels were low, anti-SARS-CoV-2 IgG was detectable and the presence of infectious virus was not demonstrated. There have also been reports of SARS-CoV-2 detection in peripheral blood mononuclear cells (PBMCs) [123] and platelets [124]. However, this appears to be rare, the levels of RNA in these cases were low and the presence of infectious virus was not demonstrated. In summary, RNAaemia is not detectable in most COVID-19 patients, is low level, brief and may not represent infectious virus.

A number of studies have reported SARS-CoV-2 antibody seroconversion times relative to time of symptom onset with mean/median times varying from 5–11 days for total antibody, 8–14 days for IgM and 10–14 days for IgG [125–130]. Neutralizing antibodies become detectable within 10–15 days of symptom onset and correlate with total antibody levels [129]. Severe COVID-19 is associated with higher levels of antibody compared to mild cases [130,131]. Long-term serological studies are not yet possible, but initial studies have indicated that IgM declines from about 2 weeks post-symptom onset. One study reported the loss of detectable IgG within 2 months [132], but most reports indicate that while IgG levels decline after approximately 2 months, levels remain relatively high for several months [131,133,134]. Assuming that detectable RNAaemia represented infectious virus, it would be expected that blood would no longer be infectious once rising titres of IgG or total antibody become detectable and viral RNA levels declined. This is indicated by a study of COVID-19 patients who were plasma RT-PCR-positive. Using a fitted curve, the plasma RT-PCR-positive rate in samples from the patients was> 90% for samples taken 1–3 days post-symptom onset but declined to <50% by 14 days [127].

Implications for safety and sufficiency of the blood supply

Broadly, emerging infectious disease (EID) pathogens can be classified into two categories. Firstly, those that are vector-borne, with limited or no human-to-human transmission. Secondly, those that are spread predominately human-to-human, such as respiratory viruses. Both categories of pathogen may impact blood safety due to the potential transfusion-transmission risk and the sufficiency of the blood supply due to infected donors/staff being unwell and unable to donate/attend work, or the loss of donors due to deferrals or social disruption. Pathogens that are predominately transmitted human-to-human may also impact sufficiency of supply due to donors being reluctant to attend donor centres out of fear of being infected. In this section, we will assess the likelihood that SARS-CoV-2 can be transmitted by transfusion and then summarize some of the strategies that blood centres can use to mitigate any potential risk to blood safety and supply.

Transfusion-transmissibility

The following criteria have been used to assess if an EID pathogen is a potential risk to blood safety: (1) able to establish infection in humans and spread within populations, (2) infection includes an asymptomatic blood phase, (3) able to survive during blood processing and storage, (4) transmissible by the intravenous route and (5) associated with a clinically apparent disease in at least a proportion of recipients [135].

As noted in the first part of this review, it is now clear that SARS-CoV-2 can establish infection in humans and cause disease (COVID-19), which may result in severe symptoms and death, and also spread efficiently from human-to-human within populations. Although SARS-CoV-2 RNA has been detected in respiratory swabs of asymptomatic patients [64,136], it has not been determined if SARS-CoV-2 infection includes an asymptomatic blood phase, either the pre-symptomatic period for infections that become symptomatic or during the course of infection in cases that do not develop symptoms. However, the absence of reported cases of SARS-CoV-2 RNA detection in the blood of asymptomatically infected individuals may be due to infrequent testing of blood as respiratory swabs are primarily used for laboratory diagnosis, most cases referred for laboratory testing are symptomatic and the potential viraemic period is probably brief and low level. The relative viral loads in the different constituents of blood, and whether viable SARS-CoV-2 is able to survive during blood processing and storage (for fresh products) has also not been determined. Similar to other human coronaviruses (including SARS-CoV and MERS-CoV), transfusion transmission of SARS-CoV-2 has not been reported [137–140], suggesting that transfusion transmission of coronaviruses is rare, if it occurs at all. However, it is acknowledged that SARS-CoV-2 has only recently been identified and therefore future reporting of transfusion-transmitted cases cannot be excluded.

Several studies have reported results of SARS-CoV-2 RNA testing of blood donors. A study of seven Korean donors, identified as COVID-19 cases post-donation, failed to detect SARS-CoV-2 RNA in repository samples from all donors [141]. In addition, platelets and red cells from

some of these donors were transfused, but no recipients had developed COVID-19 symptoms between 19–29 days post-transfusion. A study of blood donor screening/retrospective testing at the Wuhan Blood Center reported detectable RNAaemia in four donors [142]. However, these results should be interpreted with some caution. The RT-PCR results showed weak signals, indicating low levels of RNA and the possibility of false-positive results or assay contamination cannot be excluded. A case of a patient with very severe aplastic anaemia who received an apheresis platelet transfusion from a donor diagnosed with COVID-19 three days after donation has been reported [143]. There was no evidence of transfusion transmission as the recipient tested negative on follow-up testing and did develop symptoms. A report of SARS-CoV-2 RNA blood donor screening and retrospective testing in Wuhan on donor samples collected during January found 4 of 7425 donors were RNA-positive. In all cases, RNA was present at low levels and infectious virus was not confirmed [144]. A subsequent report of SARS-CoV-2 RNA screening of 94 342 blood donations in Hubei Province between 9 February and 30 April 2020 found no RNA-positive donations [145]. However, it was noted that this testing period was immediately after the height of the COVID-19 outbreak in Hubei. A Chinese study has estimated the number of donors who may have donated while in the COVID-19 incubation period for the period through to the 17 March [146]. Although the number of potentially infected donors in the incubation period was low (4·05 for the whole of China), it should also be noted that only a small proportion of window period cases would likely have detectable viral RNA and, as noted, it has not been established that infectious virus circulates in the blood.

Risk mitigation strategies

As noted, a majority of SARS-CoV-2 infections probably result in symptomatic infections with a relatively short incubation period. Donors with symptomatic infection, if presenting to donate, would be deferred from donating. In addition, blood donors should be encouraged to notify the blood centre if they develop symptoms post-donation, such as fever in the two days post-donation or sudden taste or smell dysfunction, a strategy that would partly mitigate any theoretical transfusion-transmission risk associated with donors in the incubation period but more importantly, allows contact tracing to occur if required.

For countries that have either not reported SARS-CoV-2 cases or have small clusters of human-to-human transmission (i.e. no sustained human-to-human transmission), the potential SARS-CoV-2 transfusion-transmission risk can be reduced by travel-related donor deferrals, especially in the initial phase of the epidemic when most cases are imported. Blood centres in these countries can implement a deferral, either for donors returning from countries assessed as high risk for SARS-CoV-2 infection or, given that most countries are now affected by SARS-CoV-2, all donors returning from overseas. As the epidemic progresses in a particular geographical region with sustained widespread local transmission, travel-related deferrals will be less effective in mitigating transfusion-transmission risk, especially if government closes the borders to overseas travellers and imposes a period of isolation for returning citizens [147]. A deferral for donors infected with or potentially exposed to SARS-CoV-2 can be implemented to further reduce any potential transfusion-transmission risk. For example, the WHO, US FDA and Asia Pacific Blood Network (ABPN) guidelines recommend a deferral period of 28 days for donors after possible exposure and the deferral of recovering confirmed cases of SARS-CoV-2 for at least 28 days after symptom resolution [148–150]. For convalescent plasma donors, the US FDA has recommended that a period of at least 14 days after resolution before the donation [151].

Other potential risk mitigation strategies that can be used to reduce the transfusion-transmission risk of emerging infectious diseases include pathogen reduction technologies (PRTs), donor laboratory screening and quarantine of blood components with delayed release if there is no subsequent illness reported by the donor [152–154]. Commercial PRTs are effective for MERS-CoV and SARS-CoV and at least one is effective for SARS-CoV-2 [155–157]. However, for countries that have not already implemented PRTs, it is unlikely to be a cost-effective strategy, particularly as transfusion transmission of SARS-CoV-2 has not been reported [139,158]. For each country, the implementation of blood donor screening for SARS-CoV-2 would require a validated assay approved by that country's regulator and, at present, this is not an option for most countries. In addition, given the low risk, if any, of transmitting SARS-CoV-2 by transfusion, implementing a donor screening assay would not be cost-effective. Quarantining of components would be difficult to implement operationally and, particularly if there is widespread transmission of SARS-CoV-2, could potentially impact the sufficiency of supply. In addition, quarantining platelets would not be feasible due to the short shelf life.

Sufficiency of supply and proportionate response

The response by blood centres to outbreaks and epidemics should be proportionate to the level of risk to both recipients and sufficiency of supply [150,159]. Decisions about implementing donor travel deferrals need to balance the safety and sufficiency of the blood supply. For example,

the deferral of donors will result in the loss of product in the short term and, potentially in the longer term, donors. The deferral of blood donors can have adverse psychological impacts on donors and negatively impact future donation intention [160,161]. In addition, it is important that both blood centres and government health departments carefully manage their response to infectious disease outbreaks, taking care not to create undue concern among donors and the general population as donors may be reluctant to attend donor centres due to a fear of being infected and/or reluctance to travel due to restrictions [162–165]. Therefore, it is important for blood centres to take appropriate measures to mitigate the risk of SARS-CoV-2 transmission in donor centres, as this will reassure donors and minimize the risk of transmission to staff. A potential measure to maintain donor numbers is to relax existing donor deferrals, where it is demonstrably safe to do so. For example, the US FDA has recently recommended a relaxation of donor deferrals relating to sexual activity [166]. Attracting and selecting suitable donors is an important challenge, given that convalescent plasma [167–169], intravenous immunoglobulin (IVIG) and hyperimmune globulin [170,171] are being investigated as potential treatment options for COVID-19.

Conclusions

For countries without a substantial number of reported cases or where most cases are imported, the potential transfusion-transmission risk associated with SARS-CoV-2 could be reduced by the implementation of deferral policies relating to potential geographical exposure, a history of SARS-CoV-2 infection or potential local exposure to SARS-CoV-2 cases. For countries with widespread and sustained local transmission, in addition to the deferral of confirmed cases and those potentially exposed, PRT may be an option to reduce the transfusion-transmission risk, but each country would need to perform its own risk assessment to determine the cost-effectiveness. However, based on current knowledge of SARS-CoV-2 infection and the absence of reported transfusion transmission of coronaviruses, the risk of transmitting SARS-CoV-2 by transfusion appears to be low or may not occur at all. If it does occur, the risk is certainly substantially lower than the respiratory route. Accordingly, the biggest risk to blood services in the current COVID-19 pandemic is to maintain the sufficiency of the blood supply, including adequate provision of plasma, while minimizing respiratory transmission of SARS-CoV-19 to donors and staff while donating blood.

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Conflict of interests

The authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.