Is SARS-CoV-2 transfusion transmitted?

A number of published studies report that the RNA of SARS-CoV-2, the virus causing pandemic COVID-19, is detected in the blood, plasma, or serum of infected people.[1–3] Unsurprisingly, some of these reports include RNA detection in blood donors.[4,5] This gives rise to the obvious question: Is SARS-CoV-2 a transfusion-transmitted infection (TTI)? If it is, does it cause a transfusion-transmitted disease (TTD)? We do not know; we think it is unlikely, but we have not proven the negative.

There is no precedent for transmission of any respiratory virus by the parenteral route, including this century's two serious emergent coronaviruses (SARS, the severe acute respiratory syndrome coronavirus, and MERS, the Middle East respiratory syndrome coronavirus). The U.S. Food and Drug Administration has said "The potential for transmission of SARS-CoV-2 by blood and blood components is unknown at this time. However, respiratory viruses, in general, are not known to be transmitted by blood transfusion, and there have been no reported cases of transfusion-transmitted coronavirus."[6] In keeping with this position, the European Centre for Disease Prevention and Control, while recognizing TTI as a risk that "remains theoretical but cannot be completely excluded," focuses its rapid risk assessment recommendations about substances of human origin on maintaining a robust blood supply for ongoing transfusion needs and related business continuity imperatives.[7]

Four things are needed for a pathogen to cause a TTI.[8] First, the agent must be present in the blood of a donor who can be qualified to donate, that is, who feels well and healthy on the day of donation and is able to pass our screening examination and interview. Second, it must survive in the collected component(s). Third it must find susceptible cells to infect and in which to proliferate. Finally, to be a TTD it must make the recipient ill.

1. SARS-CoV-2 RNA can be amplified from blood in both ill and asymptomatic donors (let us call this "RNA-emia").[4,5] We have no idea at this early date, however, whether and to what extent this RNA is a valid surrogate for the presence of *infectious viremia* (despite the frequent incautious and imprecise use of the two terms interchangeably). RNA from related coronaviruses that cause SARS and MERS has also been found in blood and outside the respiratory tract but infectious virus is not described.[9–11]
2. I can find no published data on survival of any infectious coronavirus, including SARS-CoV-2, during the shelf life of blood components associated with their individual storage conditions, although tissue culture infectious SARS and MERS-CoV survive briefly in control units from spiking studies that are used to validate the effect of pathogen reduction systems on individual pathogens.[12–14] Unpublished data suggest the same for SARS-CoV-2 (S. Keil, TerumoBCT, personal communication, April 9, 2020).
3. Apparently intact virions of the SARS coronavirus can be found in blood cells and extrapulmonary tissues by EM and other techniques.[15] SARS-CoV-2 infects respiratory epithelium after inoculation into the airway. It can infect a variety of tissue culture cells and organoids, including from nonrespiratory sources.[16] Accordingly, in the face of what is not known, one cannot exclude a theoretical risk of TTI.
4. Finally, to be a TTD it must cause illness in the transfused, infected recipient. Suspecting a new TTD requires our surveillance systems to recognize that an episode of disease in a transfused recipient was temporally associated with transfusion and infection in the blood donor. As noted, RNA-emia during SARS and MERS is well recognized, albeit without formal surveillance, but neither has been alleged or proven to be a TTD after 8098 cumulative SARS cases and 2519 of MERS[17,18] since their emergence (nor have other respiratory viruses, e.g., influenza A). Ideally, if and when such a relationship is postulated, molecular methods will be used to establish the identity of donor and recipient pathogen strains. We have to look for it.

Early returns suggest that from 15% to 40% of SARS-CoV-2–infected individuals have detectable RNA-emia.[1–3] Likely that range represents the timing of sampling during the natural history of infection and the sampling and assay methods used. The obvious limitation is that the data are for RNA only. The critical correlation of the of SARS-CoV-2 RNA-emia with transmissible virus (e.g., isolation of virus in culture or animal infectivity) has not been made. The few studies of SARS-CoV-2 RNA in donors or of donors developing COVID-19 after giving blood are a mix of small series wherein prospectively test-positive units were quarantined and not transfused or involved units quarantined after donation to permit the donor time to get ill before units are distributed. So, they lack transfused recipient follow-up or proof of viremia at time of donation. In Wuhan, China, four of 7425 qualified blood donors were PCR positive.[4] The samples appear to have been a mix of prospective and archived donation aliquots, the presence of RNA was not

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confirmed with alternate methods, no virus isolation was attempted, and donors were not followed up with serology. All the positive donors appear to have been collected at the peak of the Chinese epidemic in late January so even at face value the report may represent the worst case. In a lookback to recipients of 17 transfused components from seven South Korean donors who developed COVID-19 6 to 15 days after donation, there was no associated clinical morbidity in the recipients; however, archived samples tested by PCR after the donors reported their illnesses were negative.[5] This suggests that viremia was either absent or very low level on the day of phlebotomy in these asymptomatic donors. Nine mildly affected, hospitalized patients (not donors) in Germany have been described with more complete virologic characterization.[19] Blood yielded RNA from zero of 31 serum samples and was not cultured. Both RNA and tissue culture infectious SARS-CoV-2 were consistently found from upper airway and pulmonary samples. It is interesting that, despite the consistent presence of RNA in stool, no virus could be recovered, illustrating that the presence of RNA may not be a superb surrogate for infectivity. The absence of culturable virus beyond Day 8 after symptom onset in this small series may be relevant to the collection of therapeutic plasma from recovered COVID-19 patients.

Corman et al.,[20] in this issue of **TRANSFUSION**, provide RNA results from 18 SARS-CoV-2 infections. RNA-emia was present in a single patient with severe, advanced infection and acute respiratory distress syndrome (ARDS). Fourteen patients with milder COVID-19 diagnoses were RNA-negative in blood, as were all three asymptomatic infections. The latter data are reassuring regarding people well enough to donate but given the small numbers the authors request for further studies of this nature is fitting.

Presymptomatic transmission, presumed to be from virus in the upper airway, has been documented, especially in family clusters where intense, prolonged exposures occur, and asymptomatic transmission in the last 1 to 3 days of the incubation period is considered probable.[21] Precise estimates of the prevalence of asymptomatic/presymptomatic infection and especially of whether RNA-emia or, more germane to this topic, viremia occur in the absence of illness (especially in healthy donors or the larger well population who might be qualified to donate) are among the key missing data needed to inform our debate about any risk of TTI and subsequent TTD.

In the same vein, since the onset of the epidemic, given the more than one million confirmed cases and estimates that anywhere from 5% to 80% of infections are not being recognized and confirmed with a laboratory test, there must have been a nontrivial number of RNA-emic units collected and transfused without reports yet of a suspected TTD (reviewed in Heneghan et al.[22]) But what is our index of suspicion for recognition of TTD? How would we recognize it if it happened in the face of exponentially increasing caseloads in stressed acute health care venues? This is analogous to the difficulty in assessing the clinical significance of transfusion-transmitted dengue coincident with extensive vector transmission during its explosive seasonal epidemics.[23] Would the clinical picture resemble that of respiratory infection when parenterally transmitted? Can we mine the electronic medical records of hospitalized COVID-19 patients and appropriate controls in high-incidence communities for a history of recent transfusion? When there is no statistical association of transfusion with SARS-CoV infection would such information suffice to "prove" the negative?

So, what are our options?

1. Keep obtaining data. Unlike a few of my more precautionary colleagues, I do not believe that asking for more data is the "last refuge of a scoundrel"(with abject apologies to Samuel Johnson). The data will include, for example, donor RNA prevalence and incidence studies being planned as this is written, including large, longitudinal unlinked donor testing studies using investigational molecular assays (M. Busch, personal communication, April 10, 2020). Vigorous attempts are needed to isolate the virus from donated blood and/or demonstrate its infectivity in animal models and/or tissue culture when RNA-positive donors are identified.
   Given that establishing clinical suspicion for an episode of TTD at the bedside will be daunting in the face of an enormous, explosive epidemic, data-mining techniques should be considered, interrogating the huge repositories of clinical information stored in electronic medical records and maintained by health care payors and so forth, seeking an association of transfusion with a subsequent episode of care or positive test result for the virus. Any signal would be investigated for plausibility and causality.
2. We should continue our instructions to otherwise healthy donors with potential exposures or who are under investigation that they refrain from donation for appropriate intervals. Would it enhance our approach to donor call-back for development of illness from 2 to 4 days to longer? This requires understanding the kinetics of any purported potentially infectious viremia to protect recipients (and infectivity by the respiratory route to protect staff). Current evidence suggests respiratory transmission only quite late in the clinical incubation period, but these efforts cannot eliminate risk from truly asymptomatic infections.
3. Pathogen reduction is not ready for prime time given the clinical, operational, and regulatory difficulties of implementation at scale, especially in the midst of our pandemic response. That said, we now have another emerging infection to cite to convince the companies, the regulators, blood collection facilities, and end users how important it really is as a foundational strategy in the future.
4. Donor RNA screening, in the absence of historical precedent or current credible clinical suspicion for COVID-19

as a TTD, seems premature. We lack high-throughput RNA assays validated on blood specimens and have far more urgent needs to address first, especially where diagnostic and population surveillance testing capacity shortfalls persist. Additionally, donor testing is likely to result in test seeking by those interested in being tested who have not been able to access it in clinical venues. We have little idea of the correlation of infectivity with RNA-emia and in the midst of our more important task of marshaling a sustained blood supply during the pandemic, donor testing seems not to be the best use of collection facility people, time, or fiscal resources. So, I fall back on 1—get the data.

As is always the case, judicious transfusion practice is among the most important measures for decreasing TTI/TTD risk. It is no surprise that our colleagues in the bleeding disorders community have addressed their risk of SARS-CoV-2 TTD from labile components most appropriately: "treatment decisions should be based on clinical risk/benefit analysis balancing the safety of not treating a bleeding event and any residual risk of acquiring another infection."[24]

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CONFLICT OF INTEREST

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