Prevalence and clinical relevance of viraemia in viral respiratory tract infections: a systematic review

Karl Hagman*, Tamara Postigo*, David Diez-Castro*, Johan Ursing, Jesús F Bermejo-Martin†, Amanda de la Fuente†, Ana P Tedim†

In this Review, we analysed the prevalence of viraemia during infection with SARS-CoV-2 and other relevant respiratory viruses, including other human coronaviruses such as MERS-CoV and SARS-CoV, adenovirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A and B virus, parainfluenza virus, and respiratory syncytial virus. First, a preliminary systematic search was conducted to identify articles published before May 23, 2024 that reported on viraemia during infection with respiratory viruses. The articles were then analysed for relevant terms to identify the prevalence of viraemia, its association with the disease severity and long-term consequences, and host responses. A total of 202 articles were included in the final study. The pooled prevalence of viraemia was 34% for SARS-CoV-2 and between 6% and 65% for other viruses. Association of viraemia with disease severity was extensively reported for SARS-CoV-2 and also for SARS-CoV, MERS-CoV, adenoviruses, rhinoviruses, respiratory syncytial virus, and influenza A(H1N1)pdm09 (albeit with low evidence). SARS-CoV-2 viraemia was linked to memory problems and worsened quality of life. Viraemia was associated with signatures denoting dysregulated host responses. In conclusion, the high prevalence of viraemia and its association with disease severity suggests that viraemia could be a relevant pathophysiological event with important translational implications in respiratory viral infections.

Introduction

Viraemia is a crucial and well documented pathogenic event in systemic infections, such as those caused by measles virus and varicella zoster virus.[1,2] Even though the primary route of infection for these viruses is through the respiratory tract, the viruses lead to a systemic infection in immunologically naive individuals, resulting in symptoms associated with a wide range of organs. The experience with COVID-19 has indicated that viraemia can also play an important role in viral infections that primarily affect the respiratory tract.

The lungs represent an anatomical site where the target cells for respiratory viruses (alveolar epithelial cells) interact closely with vast networks of blood capillaries, as well as the cells mediating the host response against these viruses. In a host unable to control viral replication at an early stage, the inflammatory response, activation of the coagulation system or direct action of the virus, or both, could damage the alveoli and vascular endothelium. This effect can lead to leakage of virions or viral components into the pulmonary and systemic circulation, potentially spreading the damage to other parts of the lungs and distant organs.[3,4]

The prevalence and clinical relevance of viraemia secondary to respiratory infections caused by viruses other than SARS-CoV-2 remain largely unknown, partly attributed to viraemia not being recognised as an important occurrence during infections caused by respiratory viruses, compounded by the difficulty in culture isolation of respiratory viruses from the blood.[5] Nonetheless, RNAaemia or antigenaemia could serve as surrogates of viraemia. Evidence has shown that the presence of viral material in the blood reflects the degree of viral replication in the lungs.[6,7]

In this systematic review, we collected and analysed the evidence in existing literature on the prevalence of viraemia during infections caused by respiratory viruses. In this Review, viraemia was defined as the presence of live virus or viral components in the blood. We also described the short-term and long-term clinical effect and host-response alterations linked to viraemia. Finally, we discussed the translational implications that profiling viraemia could have in this context.

Methods

Search strategy and selection criteria

We performed a systematic search in PubMed, compliant with the PRISMA guidelines, on the most important respiratory viruses from database inception until May 23, 2024, as follows: adenovirus; human coronaviruses, including MERS-CoV, SARS-CoV, and SARS-CoV-2; human metapneumovirus; human rhinovirus or enterovirus; influenza A and B virus; parainfluenza virus; and respiratory syncytial virus (RSV), which are the most prevalent respiratory viruses routinely assessed in microbiology laboratories.[8] All the possible variations for the names of these viruses were covered in PubMed using the following search query: "AND ((viremia) OR (viraemia) OR (RNAemia) OR (antigenemia) OR (antigenaemia) OR ("viral particle" AND (blood OR plasma OR serum OR sera)) OR ("viral particles" AND (blood OR plasma OR serum OR sera)) OR (("viral load") AND (blood OR plasma OR serum OR sera))) AND ((patient OR patients OR person OR people OR individual OR individuals OR participant OR participants OR volunteer OR volunteers)) NOT (Review[Publication Type] OR "Case reports"[Publication Type]))".

We identified a total of 2865 articles. Only articles in English were considered. Using the PMID, we excluded duplicate articles that appeared in more than one search, ending up with a total of 2448 articles. Screening of these

Lancet Microbe 2024

Published Online
https://doi.org/10.1016/j.lanmic.2024.100967

*Joint first authors
†Contributed equally

Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden (K Hagman MD); **Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden** (K Hagman); **Group for Biomedical Research in Respiratory Infection & Sepsis (BioSepsis), Instituto de Investigación Biomédica de Salamanca (IBSAL), Gerencia Regional de Salud de Castilla y León, Salamanca, Spain** (T Postigo MSc, J F Bermejo-Martin MD, A de la Fuente MSc, A P Tedim PhD); **Department of Anatomy and Histology** (D Diez-Castro MSc) **and Department of Medicine** (J F Bermejo-Martin), **Faculty of Medicine, University of Salamanca, Salamanca, Spain; Group for Biomedical Research in Neuroendocrinology and Obesity, IBSAL, University of Salamanca, Salamanca, Spain** (D Diez-Castro); **Department of Infectious Diseases** (J Ursing MD) **and Department of Clinical Sciences** (J Ursing), **Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden; Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES, CB22/06/00035), Instituto de Salud Carlos III, Madrid, Spain** (J F Bermejo-Martin, A de la Fuente, A P Tedim)

Correspondence to:
Dr Jesús F Bermejo-Martin, Department of Medicine, Faculty of Medicine, University of Salamanca, Salamanca 37007, Spain
jfbermejo@usal.es

For more on the **PRISMA reporting guidelines** see https://www.prisma-statement.org

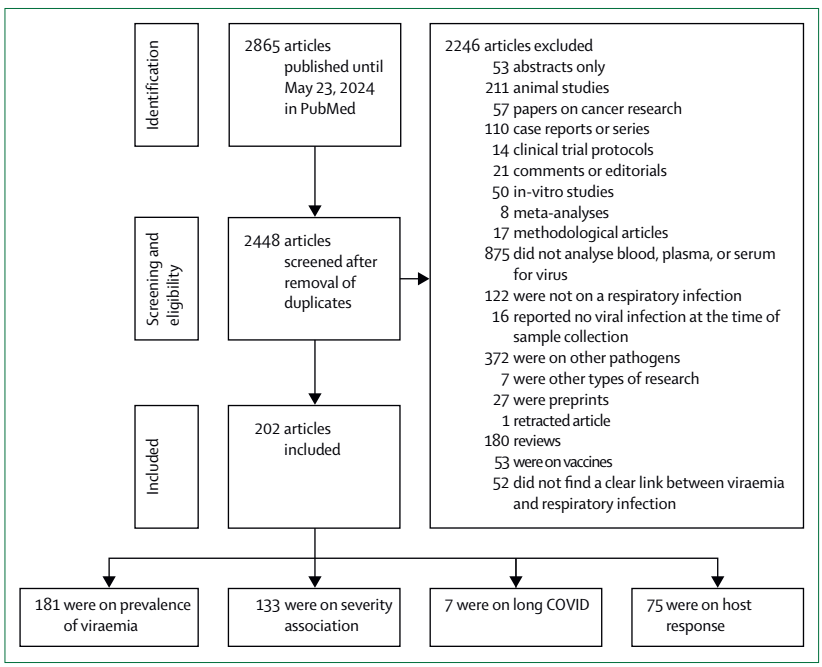

Figure 1: **PRISMA flow diagram of the study selection**

See Online for appendix

articles for relevance resulted in the exclusion of 2246 of them (the exclusion criteria are provided in figure 1 and appendix pp 19–52). Finally, a total of 202 articles were included in this Review.

Data analysis

The articles finally included in the review were screened to identify those evaluating the prevalence of viraemia in the acute phase of the disease. The summary prevalence (95% CI) of viraemia for different respiratory viruses was calculated by random effects meta-analyses using Freeman–Tukey double-arcsine transformation[9] on data from adults and children. A forest plot was created to summarise the data from a subanalysis of the prevalence of RNAaemia during SARS-CoV-2 infection in individuals with varying disease severity at the time of sampling (appendix p 16). The heterogeneity among studies was assessed using chi-squared statistics and the I^2 value.[10] Statistical analyses were performed using Stata version 18.0. A p-value of less than 0·05 was considered statistically significant.

Furthermore, articles were screened for the association between viraemia and disease severity in the acute phase of the disease. Six variables of severity were considered for this objective, as follows: [Severity SCORES], encompassing the severity of the disease as assessed by clinical scores or guidelines; [Hospital admission], which indicated whether patients required admission to a hospital; [Extrapulmonary complications], which included the terms "Multiple organ dysfunction/failure", "Myocardial Injury", "Severe Liver Dysfunction", "Renal Replacement Therapy", or "Extrapulmonary Complications"; [Respiratory involvement with no Acute Respiratory Distress Syndrome (ARDS)], which included the terms "Necessity of Oxygen therapy", "Hypoxemia", "Chest x-ray abnormalities", and "Respiratory Failure" in the absence of ARDS; [Severe/Critical Status], which included the terms "ICU admission", "Necessity of mechanical ventilation or Extracorporeal membrane oxygenation, ECMO", "ARDS" (in COVID-19, this variable also includes "Severe disease", as classified by WHO[11] with a severity score ranging from 6 to 10; however, in some studies, only the WHO score was mentioned); and [Mortality].

The articles were also screened for the following terms to evaluate the correlation of viraemia with long-term consequences: [long COVID], [post COVID], [post-acute COVID-19], [post-acute sequelae of COVID-19], [PASC], [MIS-C], and [long-term consequences]. Moreover, articles were screened for the presence of the following terms to identify those evaluating the link between viraemia and the host response: [cytokine/s], [chemokine/s], [interleukin/s], [interferon/s], [defensin/s], [complement factor/s], [perforin/s], [leukocyte/s], [neutrophil/s], [proteases], [lymphocyte/s], [monocyte/s], [dendritic cells], [T cells], [B cells], [antigen presentation], [immunoglobulin/s], [IgG], [IgA], [IgM], [T regulatory cells (Treg)], [natural killer cells (NK)], [neutrophil extracellular traps (NETs)], [endothelial dysfunction], [Vascular cellular adhesion molecule-1 (VCAM-1)], [Angiopoietin-2 (ANG2)], [Endothelin-1 (ET-1)], [D-dimer/s], [platelets], [proteomics], [RNA-seq], [coagulation], and [inflammation].

Critical appraisal

All studies that met the inclusion criteria for the sections on prevalence and disease severity were evaluated individually by two independent reviewers (DD-C and TP) to assess the risk-of-bias using The Joanna Briggs Institute (JBI) critical appraisal checklist[12,13] and Newcastle–Ottawa quality assessment Scale (NOS)[14,15] (appendix pp 3–5).

For the JBI checklist, the final scores ranged between 0 and 9, classifying each article into one of the following categories: low risk-of-bias (7–9 points), moderate risk-of-bias (5–6 points), and high risk-of-bias (<5 points). Final NOS scores ranged between 0 and 8, classifying the articles into the following three categories: low risk-of-bias (8 points), moderate risk-of-bias (7 points), and high risk-of-bias (<7 points). Regardless of the scores, all studies were included in the main analyses.

Results

There are few data available in the literature on the prevalence of viraemia in acute viral respiratory tract infections. The available studies (n=181) suggest that viraemia is a common feature for SARS-CoV-2 (n=122) and other viruses (n=59) that cause respiratory tract infections (table and appendix pp 53–57).[4–6,16–192]

Regarding the risk-of-bias assessed by JBI for articles on SARS-CoV-2 included in this section, the majority of articles (n=92, 75%) were categorised as having a low risk-of-bias, followed by those that had a moderate risk-of-bias (n=30, 25%),

Virus	Viral component	All patients				Adults				Children			
		Patients viraemic	Patients sampled	Percent viraemic (95% CI)	Number of studies	Patients viraemic	Patients sampled	Percent viraemic (95% CI)	Number of studies	Patients viraemic	Patients sampled	Percent viraemic (95% CI)	Number of studies
Adenovirus	DNA	157	410	57% (24–87)	7	14	16	90% (68–100)	2	143	394	44% (11–80)	5
Enterovirus	RNA	12	28	43% (25–62)	1	..	..	..	0	12	28	43% (25–67)	1
Seasonal influenza A/B	RNA	20	212	6% (1–13)	10	16	132	10% (2–21)	5	4	80	3% (0–11)	5
Influenza A H1N1 (2009)	RNA	58	373	16% (3–35)	9	57	263	17% (3–39)	8	1	10	10% (0–38)	1
Avian influenza*	RNA	32	62	54% (19–88)	5	20	43	43% (3–89)	4	3	3	100% (50–100)	1
Rhinovirus	RNA	124	1400	8% (3–15)	6	4	223	4% (0–30)	2	120	1178	10% (6–16)	5
RSV	RNA	105	313	29% (13–49)	5	32	133	20% (4–43)	2	73	180	36% (12–65)	3
	Antigen	9	15	60% (34–84)	1	..	..	..	0	9	15	60% (34–84)	1
Human CoV†	RNA	0	20	0% (0–8)	1	..	..	..	0	0	20	0% (0–8)	1
MERS-CoV	RNA	80	145	58% (43–72)	6	80	145	58% (43–72)	6	..	..	..	0
SARS-CoV	RNA	156	250	65% (54–75)	9	149	242	63% (52–74)	8	7	8	88% (54–100)	1
	Antigen	80	85	94% (88–98)	1	80	85	94% (88–94)	1	..	..	..	0
SARS-CoV-2	RNA	6329	16 720	34% (29–40)	111	6271	15 800	38% (33–44)	101	49	337	7% (0–24)	9
	Antigen	1541	2741	63% (50–75)	17	1431	2566	63% (47–78)	13	110	175	63% (42–82)	4

RSV=respiratory syncytial virus. CoV=coronavirus. MERS=Middle East respiratory syndrome. SARS=severe acute respiratory syndrome. Number of patients with acute viral respiratory tract infections and tested for viraemia (RNAaemia or DNAaemia or antigenaemia). A list of the included papers is shown in the appendix (pp 53–57). Synthesised proportions of viraemic patients (95% CI) calculated via random-effects meta-analyses with the Freeman-Tukey double-arcsine transformation. Summary statistics of heterogeneity are shown in the appendix (pp 58). *Includes influenza A H5N1 and H7N9. †Includes 229E, NL63, OC43, and HKU1.

Table: **Prevalence of viraemia in acute viral respiratory tract infections**

with no articles estimated to have a high risk-of-bias (appendix p 17). In these studies, the main source of the overall risk-of-bias was an inadequate sample size (figure 2).

The prevalence of viraemia in SARS-CoV-2 infections differs depending on the sampled population (eg, disease severity), timing of the sampling, sensitivity of the method used to identify viraemia (eg, reverse transcription quantitative PCR *vs* droplet digital PCR), and the viral fragment detected (eg, RNA *vs* antigens).[4,48,86,107,161] The synthesised prevalence of SARS-CoV-2 RNAaemia in the 111 included papers was 34% (95% CI 29–40), with high heterogeneity between studies (I^2=98·2%, appendix p 58). The prevalence increased significantly (p<0·001) with disease severity at the time of sampling, as shown in data from 48 of the included studies (appendix p 16).

The prevalence of RNAaemia was 11% (95% CI 0·5–18) in patients with mild or moderate disease, 36% (26–46) in those with severe disease, and 65% (56–75) in those with critical disease. Moreover, patients with critical disease had a higher plasma RNA load than patients with milder disease.[34] Further, antigenaemia was more common and concentrations of antigen were higher in the blood of patients with severe illness compared to those with a milder course of the disease.[193] A peak concentration of RNAaemia and antigenaemia was observed during the first week after the onset of symptoms, and few positive cases were reported during the convalescent period.[133,193–196] A large majority (115 of 122) of papers reporting prevalence data on viraemia during SARS-CoV-2 infection included in this study enrolled patients during the first pandemic waves spanning from 2020 to the early months of 2021 (appendix pp 53–57).

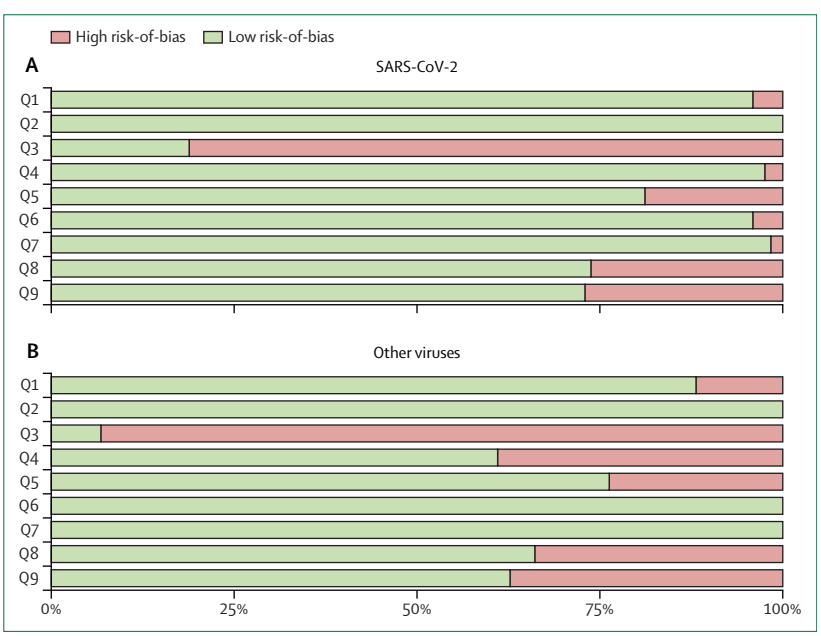

Figure 2: **Summary plots of the overall risk-of-bias assessed by means of JBI checklist of articles that studied viraemia prevalence in (A) SARS-CoV-2 infection and (B) other respiratory viral infections**
The overall risk-of-bias was presented by item as a percentage across all included studies. Items: Q1) Was the sample frame appropriate to address the target population? Q2) Were the study participants sampled in an appropriate way? Q3) Was the sample size adequate? Q4) Were the study subjects and the setting described in detail? Q5) Was the data analysis conducted with sufficient coverage of the identified sample? Q6) Were valid methods used for the identification of the condition? Q7) Was the condition measured in a standard, reliable way for all participants? Q8) Was there an appropriate statistical analysis? Q9) Was the response rate adequate, and in case not, was the low response rate managed appropriately?
JBI=The Joanna Briggs Institute.

Thus, there is a scarcity of data on the prevalence of viraemia in vaccinated or previously infected individuals. However, one study reported similar vaccination rates (36·7% *vs* 41·7%) in patients with and without antigenaemia and another reported that patients with antigenaemia were less frequently vaccinated with at least two doses.[176,192]

Data reporting the prevalence of viraemia during respiratory infections caused by other viruses were more scarce than those reporting the prevalence of viraemia during infections caused by SARS-CoV-2. In terms of risk-of-bias, most of the articles included in this study were classified as having a low risk-of-bias (n=32, 54%), followed by those having a moderate risk-of-bias (n=26, 44%), with one article classified as having a high risk-of-bias (appendix p 17). The sample size was also a key factor that affected the overall risk-of-bias (figure 2). Other important sources of risk-of-bias were inappropriate ways of reporting prevalence information and missing patient data (figure 2).

A high frequency of RNAaemia and antigenaemia (ranging from 33% to 100%) was described in patients with MERS-CoV or SARS-CoV infections.[26,28,29,31,32,36–38,43,45,68,69,72,74,77,78] Meanwhile, to the best of our knowledge, viraemia has not been described for the endemic human coronaviruses (229E, NL63, OC43, and HKU1).[71] Occasional cases of viraemia secondary to influenza virus infection have been described in presymptomatic cases.[16] Higher prevalence of RNAaemia was reported in symptomatic individuals presenting to health-care facilities compared to presymptomatic individuals, with the highest proportions observed in severely ill patients.[57,63] In adults hospitalised with influenza A(H1N1)pdm09 infection, the prevalence of viraemia was 10% (14 of 139),[57] with all patients with viraemia in the study presenting with severe disease, including six fatal cases.[57] In line with this observation, RNAaemia was found in 12% (4 of 34) of unvaccinated patients admitted to an intensive care unit (ICU) for an influenza A(H1N1)pdm09 infection.[63] RNAaemia was detected in 56% (9 of 16)[44] and 83% (5 of 6)[46] of patients hospitalised with highly pathogenic avian influenza (H5N1) infection and in 86% (12 of 14)[59], 43% (6 of 14)[65], and 0% (0 of 12)[61] of patients with H7N9 infection. RNAaemia secondary to RSV infection was common in infants, with 61% (25 of 41) of neonates with suspected RSV infection admitted to the ICU being viraemic.[21] Similarly, the prevalence of viraemia was 55% (6 of 11) in infants hospitalised for RSV infection.[21]

Higher proportions of RNAemia secondary to RSV infection were found in peripheral blood mononuclear cells than in serum samples.[20,30] RNAemia secondary to RSV infection was detected in adult haematopoietic cell transplant recipients with lower respiratory tract disease but in lower proportions compared to infants (30% [28 of 92][60] and 10% [4 of 41][50] of adults were reported viraemic). The reported prevalence of viraemia secondary to rhinovirus infection ranged between 7% and 15%.[42,56,62,75,76,81] Higher frequencies were reported in children than in adults, patients infected with the human rhinovirus C species compared to those infected by other species, and patients sampled early compared to those sampled late after the onset of symptoms.[42,56,75] Finally, studies on respiratory tract infections caused by human adenoviruses reported the prevalence of DNAemia at 16–100%.[35,66,70,80,140,178,189] Higher prevalence was described in patients with severe disease than in those with mild disease and in those infected with human adenovirus type 7 compared to other types.[35,66]

Next, a total of 133 studies that reported associations between viraemia and any of the six variables of severity detailed in the methods section were analysed.

The final NOS score for SARS-CoV-2 studies (n=94) containing information on the association of viraemia with severity classified the articles as having a moderate risk-of-bias (n=53, 57%), low risk-of-bias (n=21, 22%), and high risk-of-bias (n=20, 21%) (appendix p 18). The overall risk-of-bias mainly stemmed from the absence of regression analyses adjusted for confounding variables (figure 3).

Most studies on SARS-CoV-2 involved adult patients (88 of 94, figure 4). These 88 studies reported an association of viraemia with any of the six items of severity detailed in the methods section on 164 occasions (figure 5): 51 with [Mortality],[4,7,23,33,48,54,82,84,86,88,93,94,99,100,107,109–111,114,115,118,119,126,128,136,141,145,148,155,157,165–167,170–173,177,180,181,183,185–187,190,192,197–203] 65 with [Severe/Critical Status],[7,33,34,41,48,54,82,84,89,91,93,99,100,107,110,111,114,115,118,122,126–128,132,134,135,137,143–145,148,152,160,161,163,165,167,170–172,177,185–187,193,199–205] 18 with [Respiratory involvement with no ARDS],[23,82,86,98,107,119,128,157,158,163,167,176,181,187,190,192] eight with [Extrapulmonary complications],[23,33,116,119,129,131,161,187] four with [Hospital admission],[48,91,161,192] and seven with [Severity SCORES][23,119,138,141,183,201] (appendix pp 59–66). In contrast, these 88 studies found no association between viraemia and the six items of severity on 11 occasions [6,65,101,105,108,113,206] (figure 5 and appendix p 67).

Six of the 21 articles that involved paediatric patients focused on SARS-CoV-2 (figure 4). Four of these studies found a link between viraemia secondary to SARS-CoV-2 infection and disease severity[123,153,164,175] (appendix pp 68–69) and two others identified a trend but not an association[124,179] (appendix p 70). Viraemia secondary to SARS-CoV-2 infection seems to be more frequent in children with underlying conditions than in healthy individuals.[124,179]

The risk-of-bias evaluated in terms of the NOS score for other respiratory viruses (n=39) identified most articles as having a moderate risk-of-bias (n=21, 54%). Nevertheless, a high percentage of articles had a high risk-of-bias (n=16, 41%), and only two articles (5%) had a low risk-of-bias (appendix p 18). The risk-of-bias could mainly be attributed to the absence of appropriate statistical analyses, deficient patient follow-up, under-representation of subsets of patients (eg, recruitment of only patients admitted to the ICU), or missing data (figure 3).

Most studies on other respiratory viruses also involved adult patients (24 of 39, figure 4).

These 24 studies reported an association of viraemia with one of the six items of severity on 47 occasions (figure 5). In the cases of SARS-CoV and MERS-CoV, the little evidence available supported a link between viraemia and

different variables indicating disease severity. For SARS-CoV, we found one article indicating an association of viraemia with [Mortality], [Severe/Critical Status], [Respiratory involvement with no ARDS], [Extrapulmonary complications], and [Severity SCORES][36] and one showing an association between viraemia and [Severe/Critical Status].[28] (appendix pp 71–73). For MERS-CoV, we found two articles reporting an association of viraemia with [Severe/Critical Status] and [Mortality],[72,78] one article linking viraemia with [Mortality] alone,[68] and one reporting an association between viraemia and [Severity SCORES][74] (appendix pp 71–73). The absence of association with severity was reported once for SARS-CoV[207] and once for MERS-CoV[77] (figure 5 and appendix p 74).

For other respiratory viruses causing annual epidemics (adenoviruses, rhinoviruses, and RSV), the literature search identified a few isolated articles linking viraemia with either [Mortality],[50,60,66,70,76] [Severe/Critical Status],[50,60,66] or [Respiratory involvement with no ARDS][60] (figure 5 and appendix pp 71–73). Finally, there were mixed results on influenza, showing both the presence[51,53,57–59,63] and absence[25,47,61,65,208] of association with severity, although a clear signal indicating the effect of viraemia secondary to influenza A(H1N1)pdm09 infection on mortality was identified, with four articles showing such an association[51,53,57,58] (figure 5 and appendix pp 71–74).

Evidence on other respiratory viruses in children (15 of 21, figure 4) came mostly from five studies on rhinoviruses and three on adenoviruses. Four of the five studies on rhinovirus infection identified an association between viraemia and [Respiratory involvement with no ARDS][42,56,62,81] (appendix pp 68–69). Patients with pre-existing asthma were at higher risk of developing viraemia secondary to rhinovirus infection compared to healthy individuals.[42,75] In the case of adenovirus infection, the presence of viraemia was associated with severe pneumonia.[35,140] In addition, one study[189] found a link between higher adenovirus viral loads in the serum and an increased risk of ICU admission and mortality (appendix pp 68–69).

Studies evaluating viraemia secondary to infection with A(H1N1)pdm09, H3N2 influenza, RSV, or enterovirus in children did not identify any association with parameters of severity or disease progression[21,24,27,30,49,64] (appendix p 70). Finally, one study by De Jong and colleagues[44] that included both adult and paediatric patients with H5N1 influenza infection reported viraemia in 82% of the fatal cases (appendix pp 68–69).

Differences in the nature of the patients considered or in the methods used to profile viraemia could explain the discrepancy in the results on the association between viraemia and severity. Additional specific details on the reports evaluating the association between viraemia and disease severity are provided in the appendix (pp 6–15).

The persistence of viraemia has been linked to poorer patient outcomes than those observed without persistent viraemia. The inability to clear SARS-CoV-2 viraemia has been observed in non-survivors[88,107,109,114,145,148,170,173,198,203] and in patients with severe illness.[34,91,161,171,203] In contrast, one study found no relationship between N-antigen decline over time and disease severity.[41]

In the case of other coronaviruses, we found two studies that explored this condition in MERS-CoV infection. Patients with sustained viraemia were more likely to require ventilation support[78] and had an increased risk of death than in those without sustained viraemia.[74] In the case of adenovirus infection, two studies associated persistent viraemia with mortality.[66,70] In contrast, in the context of the avian influenza type A H7N9 virus infection, one study found no correlation between viraemia and the clinical outcome over time,[59] although the small sample size of this study could have precluded robust conclusions.

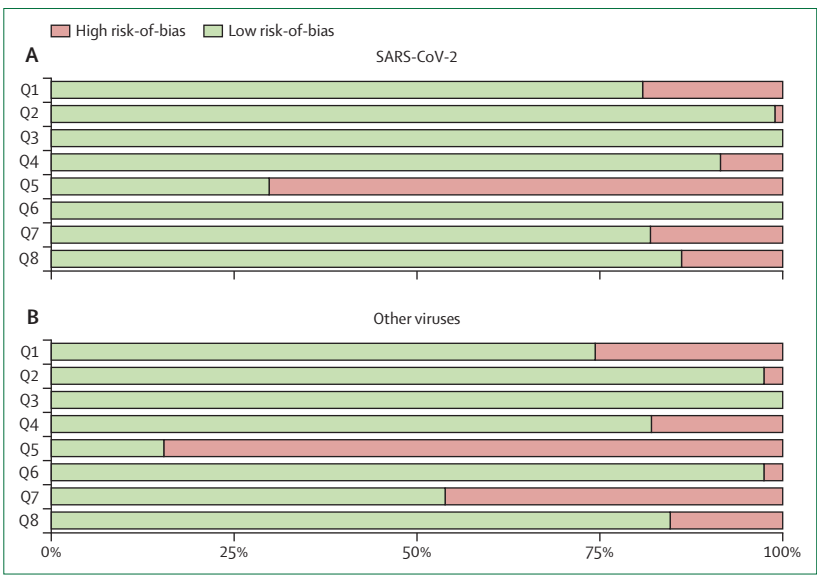

Figure 3: **Summary plots of the overall risk-of-bias assessed by a modified Newcastle–Ottawa Scale of articles that studied the association between viraemia and disease severity**
Studies on (A) SARS-CoV-2 and (B) other respiratory viruses. The overall risk-of-bias was presented by item as a percentage across all included studies. Items: Q1) Representativeness of the cohort included in the study. Q2) Viraemic and non-viraemic patients came from the same cohort of patients. Q3) Ascertainment of viraemia. Q4) Demonstration that the outcome of interest was not present at the start of the study. Q5) Statistical analysis adjusting for potential confounding variables. Q6) Assessment of outcome. Q7) Follow-up long enough for outcomes to occur. Q8) Adequacy of follow-up of cohorts.

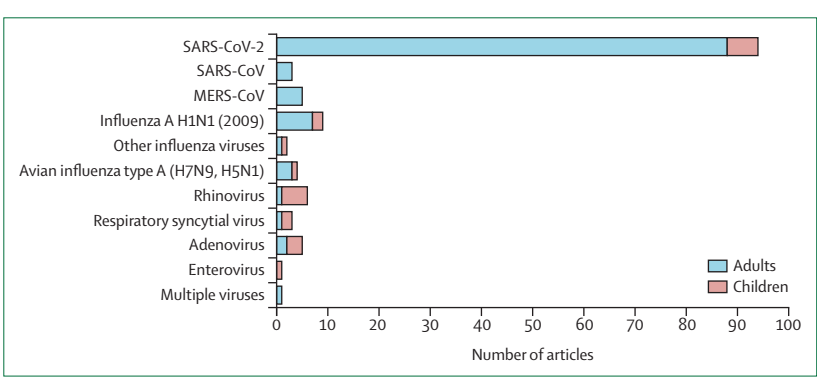

Figure 4: **Total number of articles evaluating the association between viraemia secondary to infection with respiratory viruses and disease severity, categorised by virus and type of patient (adults and children)**

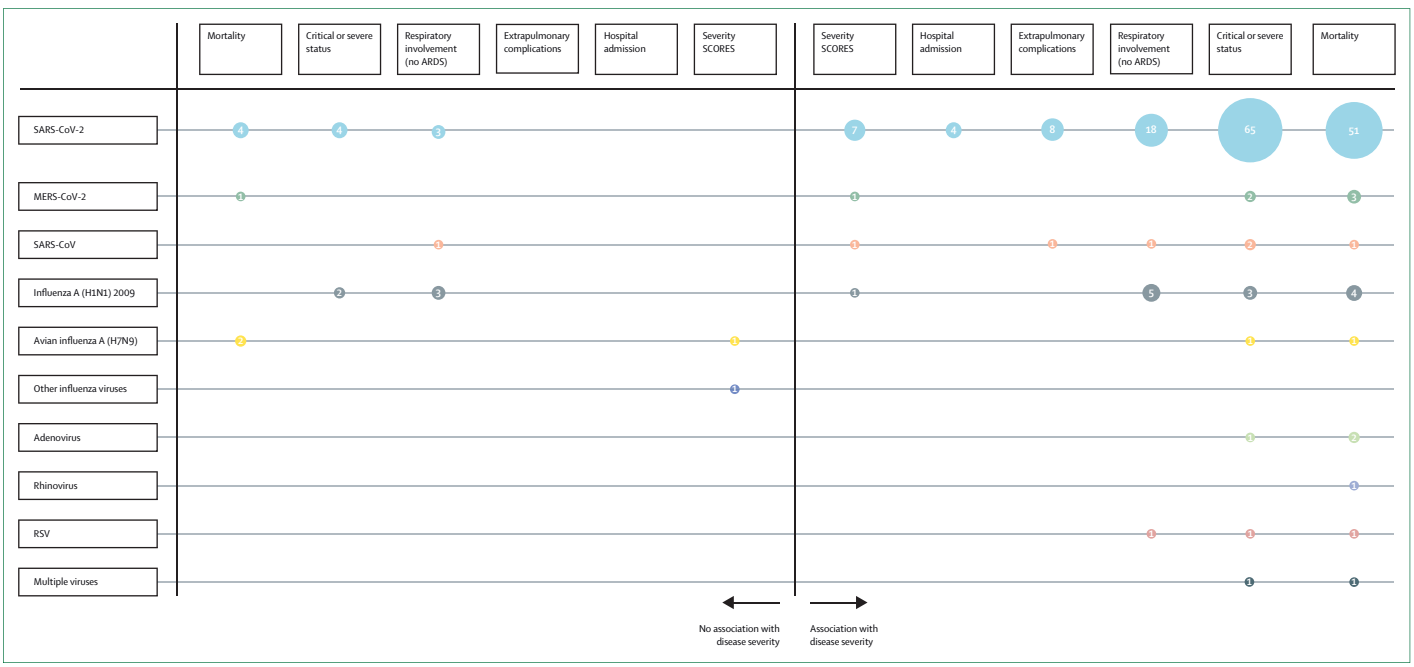

Figure 5: **Bubble plot assessing associations between viraemia secondary to infection with respiratory viruses and different variables of severity by virus in the adult population**
ARDS=acute respiratory distress syndrome. RSV=respiratory syncytial virus.

Despite the scarce data, viraemia secondary to SARS-CoV-2 infection was associated with post-COVID-19 condition (also known as long COVID) or post-acute sequelae of COVID-19 (PASC) in the seven articles that investigated this topic. SARS-CoV-2-related RNAemia at diagnosis was correlated with an increased odds of memory and concentration problems at 2–3 months after infection in a cohort (n=209) adjusted for age, sex, and disease severity.[166] In line with this finding, patients with viraemia at an emergency department (n=30) had increased odds (adjusted odds ratio 5·8, 95% CI 2·0–19·5) of disease at follow-up at a median of 35 (range 21–79) days after the onset of symptoms, as compared with those of patients without RNAemia (n=97).[160] Moreover, patients with RNAemia (n=25) reported significantly worse quality of life than patients without RNAemia (n=104), at 6 months after hospital admission.[184]

Signs of persistent viraemia have been reported in individuals with post-COVID-19 condition. Antigenaemia (mainly spike antigen) was detected in 65% (24 of 37) of the individuals with long COVID several months after the infection but infrequently in individuals who recovered after acute infection.[209] In line with this observation, S1 antigenaemia was more frequent (64% *vs* 35%) in individuals with PASC (n=22) than in individuals who never had PASC (n=17), at a median of 8 (range 1–17) months after the infection.[210] Moreover, viraemia was detected in 45% (13 of 29) of the individuals with long COVID, at a median of 55 (IQR 39–69) days after the diagnosis.[211] Children with multisystem inflammatory syndrome presented higher concentrations of antigenaemia than children with acute COVID-19.[104]

There are not enough data on the effect of viraemia on long-term complications of acute viral respiratory tract infections caused by other viruses.

The presence of viraemia during infections caused by respiratory viruses has been linked to altered host responses, and we found 75 articles (of 202) reporting such an association; most of these articles were on SARS-CoV-2 (n=57), with 18 articles reporting on other viruses. Viraemia secondary to SARS-CoV-2 infection has been associated with either leukocytosis[201] or leukopenia.[212] Nevertheless, literature clearly indicates that viraemia secondary to SARS-CoV-2 infection is paralleled by the presence of lymphopenia.[48,54,86,119,128,149,153,155,159,172,186,201,205,212,213] With respect to other white blood cells, viraemia secondary to SARS-CoV-2 infection has been associated with either neutrophilia[23,48,172,186,201] or neutropenia[155] or monocytosis[135,212] or monocytopenia.[4,48,54,110] Again, the differences in the sample sizes between these studies could explain the discrepancy in their results. Lawrence Panchali and colleagues[201] found a direct association between viraemia and the neutrophil to lymphocyte ratio. Moreover, two articles suggested that SARS-CoV-2 can infect leukocytes[187] or T lymphocytes,[214] or both.

SARS-CoV-2 viraemia is also associated with other signatures that denote an altered host response, such as higher concentrations of mediators promoting inflammation, including IL-6,[33,48,86,89,93,98,107,116,128,132,137,148,157,163,171,172,202,205,212,215] C-reactive protein,[4,23,48,54,86,98,107,119,128,149,159,167,171,172,181,186,201,205,212] procalcitonin,[23,98,128,148,205] IL-8,[4,86,93,137,148,202] tumour necrosis factor alpha,[4,48,89,132,190,202,212] IFNγ,[4,86,137,186] IFNα,[4,89,156,157,163,180] IFNλ,[93,157] C-C motif chemokine 2 (CCL2),[4,48,86,93,137,202]

ferritin,[48,98,159,172] IL-7,[48] IL-15,[4,48,93] IL-18,[120,148] IL-1 receptor-like 1,[120,148] growth/differentiation factor 15,[93,97,120] and soluble receptor for advanced glycation end-products.[93,172,202,216] One study also found an association between viraemia and decreased concentrations of the proinflammatory cytokines IL-2 and IL-9.[190] SARS-CoV-2 viraemia was also linked to high concentrations of the anti-inflammatory or immunosuppressor molecules IL-10,[48,132,135,137,148,172] programmed cell death 1 ligand 1,[4,48] IL-1 receptor antagonist protein,[48,86,93,132,202] and IL-4.[190]

The presence of SARS-CoV-2 material in the blood correlated with high concentrations of antimicrobial or antiviral molecules such as C-X-C motif chemokine 10 (CXCL10)[4,48,86,93,137,157,172] and defensin 1.[93,206] Viraemia secondary to SARS-CoV-2 infection also affected the coagulation system, as evidenced by its association with high concentrations of D-dimers[23,48,119,128,149,159,205,212] or altered platelet counts.[23,54,186] Viraemia secondary to SARS-CoV-2 infection correlated with signatures of endothelial dysfunction denoted by high concentrations of vascular cellular adhesion protein 1,[48,93] intercellular adhesion molecule 1,[48] angiopoietin-2,[48,93,202] or endothelin-1,[4] and also with tissue damage, as indicated by high concentrations of lactate dehydrogenase[23,48,54,93,119,128,149,159,172,183,186,205] and glutamic-pyruvate transaminase. Other biological markers of inflammation, renal failure, and lung and cardiac tissue injury have been found in other studies occasionally (appendix pp 75–76).

Patients with viraemia also showed increased amounts of proteins that facilitate SARS-CoV-2 infection[93] (appendix pp 75–76). Viraemia secondary to SARS-CoV-2 infection is frequently accompanied by the presence of low concentrations of antibodies against this virus, with most studies focusing on antibodies against the spike protein[4,54,83,84,100,104,107,150,151,155,163,172,193] or the antigen-receptor binding domain[100,146,150,163,167,202] and some articles reporting an association between viraemia and low anti-N antibodies.[34,54,83,91,100,107,141,150,167] In addition, the neutralisation activity of anti-SARS-CoV-2 antibodies was lower in patients with viraemia than in those without viraemia.[4,110,150,163]

There is little evidence on the effect of viraemia on host responses in the context of other respiratory viral infections. In patients with viraemia secondary to SARS-CoV infection, the appearance of anti-N antibodies is paralleled by the clearance of the N protein[31] and viral load from the blood.[32] Furthermore, in the case of SARS-CoV, the viraemia is associated with the presence of specific proteomic signatures[37,45] (appendix pp 77–78). In MERS-CoV infection, viraemia has been found to correlate inversely with anti-S antibody concentrations[74] and their neutralisation activity,[69] although Al-Abdely and colleagues found the simultaneous presence of MERS-CoV RNA and neutralising antibodies in the serum beyond 21 days after disease onset, suggesting that antibodies might not be sufficient to clear the virus.[78]

The presence of leukopenia, neutropenia, monocytopenia, or severe thrombocytopenia represents risk factors for viraemia secondary to RSV infection in haematopoietic cell transplant recipients.[60] In addition, in children, peripheral blood mononuclear cells sometimes do contain RSV antigens[17] or RNA,[20] suggesting infection of circulating immune cells by this virus. Viraemia secondary to rhinovirus infection is associated with high concentrations of leucocytes and C-reactive protein in children.[62]

In the case of influenza infection, Berdal and colleagues found a direct correlation of viraemia with the proinflammatory molecules CCL2 and IL-8[55] and the T-cell chemotactic molecule CXCL10.[55] In addition, two articles reported that patients with viraemia secondary to influenza infection presented lower platelet and leukocyte counts[57] and profound lymphopenia than in those without viraemia.[58] Finally, Koupenova and colleagues reported the presence of the virus inside activated platelets.[79]

The presence of viraemia in adenovirus respiratory infections has been associated with a high neutrophil to lymphocyte ratio[35] and increased concentrations of inflammatory biomarkers such as procalcitonin,[35] lactate dehydrogenase,[35] glutamic-oxaloacetic transaminase 1,[35] IL-5,[189] and decreased concentrations of IL-9.[189] The presence of viral DNA in the blood also correlated with high concentrations of antimicrobial and antiviral molecules such as CXCL10.[189] In addition, viraemia had an effect on the coagulation systems, with increased concentrations of D-dimers.[35]

Discussion

This systematic review showed that viraemia was a common finding for most viral respiratory tract infections in the children and adults that were sampled herein (table). This finding indicates that viraemia could play an important role in the pathogenesis of disease and the complications caused not only by SARS-CoV-2 but also other respiratory viruses. A meta-analysis of prevalence studies on SARS-CoV-2 suggested that viraemia is significantly linked to severe disease at the time of sampling (appendix p 16). In line with these findings, the highest prevalence of viraemia was found in infections caused by the most virulent viruses, such as highly pathogenic avian influenza (H5N1 and H7N9), MERS-CoV, SARS-CoV, and SARS-CoV-2.

The clinical relevance of viraemia was further supported by its negative effect on the clinical presentation and prognosis of adults with infections caused not only by emerging viruses such as SARS-CoV, SARS-CoV-2, and MERS-CoV but also by epidemic viruses such as adenoviruses, rhinoviruses, RSV, and influenza A H1N1 (2009). Results for other influenza viruses were inconclusive or absent.

Studies on children suggested the role of viraemia as a marker of respiratory failure in rhinovirus and adenovirus infections. These results support the role of viraemia in the clinical management of patients with respiratory viral infections. The presence of viraemia could serve as a potential marker of severity, allowing for early allocation of patients to the appropriate level of care (ward or ICU) and prioritising the administration of antiviral treatments.

Our results also suggest a potential therapeutic role of haemofilters that can remove viral components. Nonetheless, given the paucity of studies on respiratory viral infections other than COVID-19, additional studies are required to confirm the relationship between viraemia and disease severity.

Our study showed that the long-term consequences of respiratory viral infections with viraemia have not been thoroughly studied. The few existing studies suggest an association between viraemia secondary to SARS-CoV-2 infection during the acute phase of the disease and post-COVID-19 condition.[160,166,184] Moreover, studies indicate that a proportion of patients with PASC or long COVID have persistent viraemia.[209–211] The extent to which detectable viral RNA or antigens in the blood represent an ongoing systemically disseminated infection is unclear. However, autopsy studies of patients with COVID-19 showed widespread dissemination of viable virus to extrapulmonary tissues,[102] with signs of persistent infection for several months after acute disease in some individuals.[217] A systemic seeding of the virus during the acute phase and persistent infection could thus be a potential explanation for post-COVID-19 condition. Several randomised, controlled studies investigating the effects of antiviral treatment on patients with PASC are registered as ongoing trials. However, more studies are needed to understand whether a causal relationship exists between viraemia and the long-term consequences of respiratory viral infections.

For more information see ClinicalTrials.gov

Unfortunately, the mechanisms by which viraemia mediates severe disease and long-term consequences are largely unknown. The scarce evidence available in the literature suggests that viraemia is linked to the development of dysregulated host responses such as the hyperproduction of proinflammatory mediators (SARS-CoV-2, influenza, adenovirus), lymphopenia (SARS-CoV-2, influenza), activation of coagulation (SARS-CoV-2, adenovirus), endothelial dysfunction (SARS-CoV-2), tissue destruction (SARS-CoV-2 and adenovirus), and defective (SARS-CoV-2, MERS-CoV) or delayed (SARS-CoV) antibody responses. As mentioned in the introduction, the coexistence of hyperinflammation, activation of coagulation, and endothelial dysfunction in the lungs could favour viraemia, and viraemia could in turn promote these events, thus creating a vicious circle.

Animal models shed some light on the causes and pathogenic role of viraemia in respiratory viral infections. A recent study on a hamster model revealed that a delayed engagement of host response enabled SARS-CoV-2 viraemia, consequently leading to infection of distal organs.[218] In mice, the presence of immunomimetic SARS-CoV-2 peptides in the blood induces proinflammatory responses and could mediate tissue or endothelial injury.[219] A study on a ferret model revealed that influenza A virus H5N1 transmitted by blood transfusion negatively affects survival.[220] Moreover, a mouse model infected with H7N9 influenza virus displayed the induction of multiple organ infection and injury following viraemia.[221] Further, studies on autopsies from immunosuppressed patients with COVID-19 suggest that these individuals died due to pathological alterations caused by extensive viral replication and cellular damage throughout the body following viraemia.[136]

Our study has some limitations. The meta-analyses of viraemia prevalence showed high heterogeneity between studies (appendix p 58), thereby impairing interpretation of the synthesised prevalence. Most studies included in this Review sampled hospitalised patients, which could represent a sampling bias and a most likely overestimation of the real prevalence of viraemia. However, a substantial proportion of viraemia was reported even in patients with mild or moderate COVID-19. The prevalence of viraemia could also be affected by previous exposure to the infection. A high prevalence in infants with RSV infection could, for example, be explained by an absence of previous exposure.[21] Nonetheless, the effect of pre-existing immunity on viraemia was not evaluated in this Review. Another limitation was the impossibility to confirm whether viraemia reflects the presence of a living virus in the blood or not, given the absence of robust evidence in the literature.

In conclusion, the dissemination of viral components from the lungs to the blood (designated here as viraemia) is a frequent event with the potential to have major pathophysiological and clinical consequences in SARS-CoV-2 infection in the short term and long term and most likely also in infections caused by other respiratory viruses. Our results warrant further studies that investigate the role of viraemia monitoring, prevention, or removal to improve the detection, treatment, prognosis, and long-term complications of patients with a severe infection caused by a respiratory virus. These findings also open new avenues to investigate the role of viraemia secondary to respiratory viral infections in the pathogenesis of extrapulmonary diseases such as diabetes or autoimmune diseases.

Contributors

KH, JU, JFB-M, and APT contributed to the conceptualisation and design of the study. APT designed the search strategy and supervised the study. KH, TP, DD-C, JU, AdlF, and APT screened and selected the articles. TP and DD-C evaluated the risk-of-bias. KH, TP, DD-C, APT, and AdlF curated and interpreted the data. All authors wrote the original draft and revised and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JFB-M has a patent application on SARS-CoV-2 antigenaemia as a predictor of mortality in COVID-19. The remaining authors declare no competing interests.

Acknowledgments

This study was supported by Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES, CB22/06/00035). The grants to KH and JU for research related to COVID-19 were funded by the Gothenburg Medical Society. Salary received by KH for lecturing on COVID-19 was financed by Gothenburg University. Contract with TP was supported by Fundació La Marató de TV3 (ajudes Econòmiques a Projectes de Recerca sobre COVID-19 - La Marató 2020, 202108-30-31). Contract with DD-C is supported by the University of Salamanca and AIDS Study Group (GeSIDA). Contract with AdlF is financially supported by Instituto de Salud

Carlos III (Contratos Predocotales de Formación en Investigación en Salud, FI20/00278), co-funded by the European Social Fund: Investing in your future. Contract with APT is financed by CiberES, Instituto de Salud Carlos III, and by "Programa de donaciones estar preparados; Unión Española de Entidades Aseguradoras y Reaseguradoras (UNESPA)" (Madrid, Spain). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

References

1 de Vries RD, Mesman AW, Geijtenbeek TB, Duprex WP, de Swart RL. The pathogenesis of measles. *Curr Opin Virol* 2012; **2:** 248–55.

2 Levin MJ. Varicella-zoster virus and virus DNA in the blood and oropharynx of people with latent or active varicella-zoster virus infections. *J Clin Virol* 2014; **61:** 487–95.

3 McGonagle D, Kearney MF, O'Regan A, et al. Therapeutic implications of ongoing alveolar viral replication in COVID-19. *Lancet Rheumatol* 2022; **4:** e135–44.

4 Bermejo-Martin JF, García-Mateo N, Motos A, et al. Effect of viral storm in patients admitted to intensive care units with severe COVID-19 in Spain: a multicentre, prospective, cohort study. *Lancet Microbe* 2023; **4:** e431–41.

5 Li L, Liang Y, Hu F, et al. Molecular and serological characterization of SARS-CoV-2 infection among COVID-19 patients. *Virology* 2020; **551:** 26–35.

6 Jacobs JL, Naqvi A, Shah FA, et al. Plasma SARS-CoV-2 RNA levels as a biomarker of lower respiratory tract SARS-CoV-2 infection in critically ill patients with COVID-19. *J Infect Dis* 2022; **226:** 2089–94.

7 Ynga-Durand M, Maaß H, Milošević M, et al. SARS-CoV-2 viral load in the pulmonary compartment of critically ill COVID-19 patients correlates with viral serum load and fatal outcomes. *Viruses* 2022; **14:** 1292.

8 Schober T, Wong K, DeLisle G, et al. Clinical outcomes of rapid respiratory virus testing in emergency departments: a systematic review and meta-analysis. *JAMA Intern Med* 2024; **184:** 528–36.

9 Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist* 1950; **21:** 607–11.

10 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.

11 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; **20:** e192–97.

12 Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015; **13:** 147–53.

13 The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. Checklist for qualitative research. https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Qualitative_Research2017_0.pdf (accessed July 10, 2024).

14 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25:** 603–05.

15 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. May 3, 2021. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed July 10, 2024).

16 Khakpour M, Saidi A, Naficy K. Proved viraemia in Asian influenza (Hong Kong variant) during incubation period. *Br Med J* 1969; **4:** 208–09.

17 Domurat F, Roberts NJ Jr, Walsh EE, Dagan R. Respiratory syncytial virus infection of human mononuclear leukocytes in vitro and in vivo. *J Infect Dis* 1985; **152:** 895–902.

18 Mori I, Nagafuji H, Matsumoto K, Kimura Y. Use of the polymerase chain reaction for demonstration of influenza virus dissemination in children. *Clin Infect Dis* 1997; **24:** 736–37.

19 Tsuruoka H, Xu H, Kuroda K, et al. Detection of influenza virus RNA in peripheral blood mononuclear cells of influenza patients. *Jpn J Med Sci Biol* 1997; **50:** 27–34.

20 O'Donnell DR, McGarvey MJ, Tully JM, Balfour-Lynn IM, Openshaw PJ. Respiratory syncytial virus RNA in cells from the peripheral blood during acute infection. *J Pediatr* 1998; **133:** 272–74.

21 Rohwedder A, Keminer O, Forster J, Schneider K, Schneider E, Werchau H. Detection of respiratory syncytial virus RNA in blood of neonates by polymerase chain reaction. *J Med Virol* 1998; **54:** 320–27.

22 Xu H, Yasui O, Tsuruoka H, et al. Isolation of type B influenza virus from the blood of children. *Clin Infect Dis* 1998; **27:** 654–55.

23 Xu D, Zhou F, Sun W, et al. Relationship between serum severe acute respiratory syndrome coronavirus 2 nucleic acid and organ damage in coronavirus 2019 patients: a cohort study. *Clin Infect Dis* 2021; **73:** 68–75.

24 Ito Y, Ichiyama T, Kimura H, et al. Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. *J Med Virol* 1999; **58:** 420–25.

25 Kaiser L, Fritz RS, Straus SE, Gubareva L, Hayden FG. Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses. *J Med Virol* 2001; **64:** 262–68.

26 Grant PR, Garson JA, Tedder RS, Chan PK, Tam JS, Sung JJ. Detection of SARS coronavirus in plasma by real-time RT-PCR. *N Engl J Med* 2003; **349:** 2468–69.

27 Kawada J, Kimura H, Ito Y, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. *J Infect Dis* 2003; **188:** 690–98.

28 Ng EK, Hui DS, Chan KC, et al. Quantitative analysis and prognostic implication of SARS coronavirus RNA in the plasma and serum of patients with severe acute respiratory syndrome. *Clin Chem* 2003; **49:** 1976–80.

29 Ng LF, Wong M, Koh S, et al. Detection of severe acute respiratory syndrome coronavirus in blood of infected patients. *J Clin Microbiol* 2004; **42:** 347–50.

30 Yui I, Hoshi A, Shigeta Y, Takami T, Nakayama T. Detection of human respiratory syncytial virus sequences in peripheral blood mononuclear cells. *J Med Virol* 2003; **70:** 481–89.

31 Che XY, Hao W, Wang Y, et al. Nucleocapsid protein as early diagnostic marker for SARS. *Emerg Infect Dis* 2004; **10:** 1947–49.

32 Chen W, Xu Z, Mu J, et al. Antibody response and viraemia during the course of severe acute respiratory syndrome (SARS)-associated coronavirus infection. *J Med Microbiol* 2004; **53:** 435–38.

33 Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. *Clin Infect Dis* 2020; **71:** 1937–42.

34 Chen L, Wang G, Long X, et al. Dynamics of blood viral load is strongly associated with clinical outcomes in coronavirus disease 2019 (COVID-19) patients: a prospective cohort study. *J Mol Diagn* 2021; **23:** 10–18.

35 Chen Q, Liu J, Liang W, et al. Clinical features, replication competence, and innate immune responses of human adenovirus type 7 infection. *J Infect Dis* 2021; **223:** 1390–99.

36 Hung IF, Cheng VC, Wu AK, et al. Viral loads in clinical specimens and SARS manifestations. *Emerg Infect Dis* 2004; **10:** 1550–57.

37 Poon TC, Chan KC, Ng PC, et al. Serial analysis of plasma proteomic signatures in pediatric patients with severe acute respiratory syndrome and correlation with viral load. *Clin Chem* 2004; **50:** 1452–55.

38 Wang WK, Fang CT, Chen HL, et al. Detection of severe acute respiratory syndrome coronavirus RNA in plasma during the course of infection. *J Clin Microbiol* 2005; **43:** 962–65.

39 Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; **323:** 1843–44.

40 Wang Y, Zhang L, Sang L, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest* 2020; **130:** 5235–44.

41 Wang H, Hogan CA, Verghese M, et al. SARS-CoV-2 nucleocapsid plasma antigen for diagnosis and monitoring of COVID-19. *Clin Chem* 2021; **68:** 204–13.

42 Xatzipsalti M, Kyrana S, Tsolia M, et al. Rhinovirus viremia in children with respiratory infections. *Am J Respir Crit Care Med* 2005; **172:** 1037–40.

43 Yeh KM, Chiueh TS, Siu LK, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother* 2005; **56:** 919–22.

44 de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006; **12:** 1203–07.

45 Pang RT, Poon TC, Chan KC, et al. Serum proteomic fingerprints of adult patients with severe acute respiratory syndrome. *Clin Chem* 2006; **52:** 421–29.

46 Buchy P, Mardy S, Vong S, et al. Influenza A/H5N1 virus infection in humans in Cambodia. *J Clin Virol* 2007; **39:** 164–68.

47 Bermejo-Martin JF, Ortiz de Lejarazu R, Pumarola T, et al. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit Care* 2009; **13:** R201.

48 Bermejo-Martin JF, González-Rivera M, Almansa R, et al. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. *Crit Care* 2020; **24:** 691.

49 Arankalle VA, Lole KS, Arya RP, et al. Role of host immune response and viral load in the differential outcome of pandemic H1N1 (2009) influenza virus infection in Indian patients. *PLoS One* 2010; **5:** e13099.

50 Campbell AP, Chien JW, Kuypers J, et al. Respiratory virus pneumonia after hematopoietic cell transplantation (HCT): associations between viral load in bronchoalveolar lavage samples, viral RNA detection in serum samples, and clinical outcomes of HCT. *J Infect Dis* 2010; **201:** 1404–13.

51 To KK, Hung IF, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis* 2010; **50:** 850–59.

52 To KK, Chan KH, Li IW, et al. Viral load in patients infected with pandemic H1N1 2009 influenza A virus. *J Med Virol* 2010; **82:** 1–7.

53 Almansa R, Anton A, Ramirez P, et al. Direct association between pharyngeal viral secretion and host cytokine response in severe pandemic influenza. *BMC Infect Dis* 2011; **11:** 232.

54 Almansa R, Eiros JM, de Gonzalo-Calvo D, et al. N-antigenemia detection by a rapid lateral flow test predicts 90-day mortality in COVID-19: a prospective cohort study. *Clin Microbiol Infect* 2022; **28:** 1391.e1–5.

55 Berdal J-E, Mollnes TE, Wæhre T, et al. Excessive innate immune response and mutant D222G/N in severe A (H1N1) pandemic influenza. *J Infect* 2011; **63:** 308–16.

56 Fuji N, Suzuki A, Lupisan S, et al. Detection of human rhinovirus C viral genome in blood among children with severe respiratory infections in the Philippines. *PLoS One* 2011; **6:** e27247.

57 Tse H, To KK, Wen X, et al. Clinical and virological factors associated with viremia in pandemic influenza A/H1N1/2009 virus infection. *PLoS One* 2011; **6:** e22534.

58 Choi S-M, Xie H, Campbell AP, et al. Influenza viral RNA detection in blood as a marker to predict disease severity in hematopoietic cell transplant recipients. *J Infect Dis* 2012; **206:** 1872–77.

59 Hu Y, Lu S, Song Z, et al. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. *Lancet* 2013; **381:** 2273–79.

60 Waghmare A, Campbell AP, Xie H, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. *Clin Infect Dis* 2013; **57:** 1731–41.

61 Yu L, Wang Z, Chen Y, et al. Clinical, virological, and histopathological manifestations of fatal human infections by avian influenza A(H7N9) virus. *Clin Infect Dis* 2013; **57:** 1449–57.

62 Esposito S, Daleno C, Scala A, et al. Impact of rhinovirus nasopharyngeal viral load and viremia on severity of respiratory infections in children. *Eur J Clin Microbiol Infect Dis* 2014; **33:** 41–48.

63 Guihot A, Luyt C-E, Parrot A, et al. Low titers of serum antibodies inhibiting hemagglutination predict fatal fulminant influenza A(H1N1) 2009 infection. *Am J Respir Crit Care Med* 2014; **189:** 1240–49.

64 Imamura T, Suzuki A, Lupisan S, et al. Detection of enterovirus 68 in serum from pediatric patients with pneumonia and their clinical outcomes. *Influenza Other Respir Viruses* 2014; **8:** 21–24.

65 Shen Z, Chen Z, Li X, et al. Host immunological response and factors associated with clinical outcome in patients with the novel influenza A H7N9 infection. *Clin Microbiol Infect* 2014; **20:** O493–500.

66 Sun B, He H, Wang Z, et al. Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study. *Crit Care* 2014; **18:** 456.

67 Wootton SH, Aguilera EA, Wanger A, et al. Detection of NH1N1 influenza virus in nonrespiratory sites among children. *Pediatr Infect Dis J* 2014; **33:** 95–96.

68 Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother* 2015; **70:** 2129–32.

69 Corman VM, Albarrak AM, Omrani AS, et al. Viral shedding and antibody response in 37 patients with Middle East respiratory syndrome coronavirus infection. *Clin Infect Dis* 2016; **62:** 477–83.

70 Gu L, Qu J, Sun B, Yu X, Li H, Cao B. Sustained viremia and high viral load in respiratory tract secretions are predictors for death in immunocompetent adults with adenovirus pneumonia. *PLoS One* 2016; **11:** e0160777.

71 Jevšnik M, Steyer A, Pokorn M, et al. The role of human coronaviruses in children hospitalized for acute bronchiolitis, acute gastroenteritis, and febrile seizures: a 2-year prospective study. *PLoS One* 2016; **11:** e0155555.

72 Kim SY, Park SJ, Cho SY, et al. Viral RNA in blood as indicator of severe outcome in Middle East respiratory syndrome coronavirus infection. *Emerg Infect Dis* 2016; **22:** 1813–16.

73 Kim J-M, Kim HM, Lee EJ, et al. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. *Osong Public Health Res Perspect* 2020; **11:** 112–17.

74 Min CK, Cheon S, Ha NY, et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. *Sci Rep* 2016; **6:** 25359.

75 Lu X, Schneider E, Jain S, et al. Rhinovirus viremia in patients hospitalized with community-acquired pneumonia. *J Infect Dis* 2017; **216:** 1104–11.

76 Van Rijn AL, Claas EC, von dem Borne PA, Kroes ACM, de Vries JJC. Rhinovirus viremia in adult patients with high viral load in bronchoalveolar lavages. *J Clin Virol* 2017; **96:** 105–09.

77 Hong KH, Choi JP, Hong SH, et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax* 2018; **73:** 286–89.

78 Al-Abdely HM, Midgley CM, Alkhamis AM, et al. Middle East respiratory syndrome coronavirus infection dynamics and antibody responses among clinically diverse patients, Saudi Arabia. *Emerg Infect Dis* 2019; **25:** 753–66.

79 Koupenova M, Corkrey HA, Vitseva O, et al. The role of platelets in mediating a response to human influenza infection. *Nat Commun* 2019; **10:** 1780.

80 Schjelderup Nilsen HJ, Nordbø SA, Krokstad S, Døllner H, Christensen A. Human adenovirus in nasopharyngeal and blood samples from children with and without respiratory tract infections. *J Clin Virol* 2019; **111:** 19–23.

81 Baillie VL, Moore DP, Mathunjwa A, Morailane P, Simões EAF, Madhi SA. A prospective case-control study on the association of rhinovirus nasopharyngeal viral load and viremia in South African children hospitalized with severe pneumonia. *J Clin Virol* 2020; **125:** 104288.

82 Benotmane I, Gautier-Vargas G, Wendling MJ, et al. In-depth virological assessment of kidney transplant recipients with COVID-19. *Am J Transplant* 2020; **20:** 3162–72.

83 Dulipsingh L, Ibrahim D, Schaefer EJ, et al. SARS-CoV-2 serology and virology trends in donors and recipients of convalescent plasma. *Transfus Apher Sci* 2020; **59:** 102922.

84 Eberhardt KA, Meyer-Schwickerath C, Heger E, et al. RNAemia corresponds to disease severity and antibody response in hospitalized COVID-19 patients. *Viruses* 2020; **12:** 1045.

85 Edlow AG, Li JZ, Collier AY, et al. Assessment of maternal and neonatal SARS-CoV-2 viral load, transplacental antibody transfer, and placental pathology in pregnancies during the COVID-19 pandemic. *JAMA Netw Open* 2020; **3:** e2030455.

86 Fajnzylber J, Regan J, Coxen K, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun* 2020; **11:** 5493.

87 Gao Y, Li Q, Shi H, et al. Preliminary exploration of the cause of liver disorders during early stages in COVID-19 patients. *Front Med* 2020; **7:** 501.

88 Ghandili S, Pfefferle S, Roedl K, et al. Challenges in treatment of patients with acute leukemia and COVID-19: a series of 12 patients. *Blood Adv* 2020; **4:** 5936–41.

89 Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; **369:** 718–24.

90 Han MS, Seong MW, Kim N, et al. Viral RNA load in mildly symptomatic and asymptomatic children with COVID-19, Seoul, South Korea. *Emerg Infect Dis* 2020; **26:** 2497–99.

91 Hingrat QL, Visseaux B, Laouenan C, et al. Detection of SARS-CoV-2 N-antigen in blood during acute COVID-19 provides a sensitive new marker and new testing alternatives. *Clin Microbiol Infect* 2020; **27:** 789.e1–5.

92 Hueso T, Pouderoux C, Péré H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood* 2020; **136:** 2290–95.

93 Li Y, Schneider AM, Mehta A, et al. SARS-CoV-2 viremia is associated with distinct proteomic pathways and predicts COVID-19 outcomes. *J Clin Invest* 2021; **131:** e148635.

94 Li L, Tan C, Zeng J, et al. Analysis of viral load in different specimen types and serum antibody levels of COVID-19 patients. *J Transl Med* 2021; **19:** 30.

95 Li Y, Moser C, Aga E, et al. Immune status and SARS-CoV-2 viral dynamics. *J Infect Dis* 2023; **228** (suppl 2): S111–16.

96 Li Y, Harrison LJ, Chew KW, et al. Nasal and plasma severe acute respiratory syndrome coronavirus 2 RNA levels are associated with timing of symptom resolution in the ACTIV-2 trial of nonhospitalized adults with coronavirus disease 2019. *Clin Infect Dis* 2023; **76:** 734–37.

97 Myhre PL, Prebensen C, Strand H, et al. Growth differentiation factor 15 provides prognostic information superior to established cardiovascular and inflammatory biomarkers in unselected patients hospitalized with COVID-19. *Circulation* 2020; **142:** 2128–37.

98 Myhre PL, Prebensen C, Jonassen CM, Berdal JE, Omland T. SARS-CoV-2 viremia is associated with inflammatory, but not cardiovascular biomarkers, in patients hospitalized for COVID-19. *J Am Heart Assoc* 2021; **10:** e019756.

99 Nijhuis RHT, Russcher A, de Jong GJ, et al. Low prevalence of SARS-CoV-2 in plasma of COVID-19 patients presenting to the emergency department. *J Clin Virol* 2020; **133:** 104655.

100 Röltgen K, Powell AE, Wirz OF, et al. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. *Sci Immunol* 2020; **5:** eabe0240.

101 Schlesinger T, Weißbrich B, Wedekink F, et al. Biodistribution and serologic response in SARS-CoV-2 induced ARDS: a cohort study. *PLoS One* 2020; **15:** e0242917.

102 Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020; **173:** 268–77.

103 Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. *J Pediatr* 2020; **227:** 45–52.e5.

104 Yonker LM, Gilboa T, Ogata AF, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *J Clin Invest* 2021; **131:** e149633.

105 Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang Province, China, January–March 2020: retrospective cohort study. *BMJ* 2020; **369:** m1443.

106 Zhou X, Wang G, Chen L, et al. Clinical characteristics of hematological patients concomitant with COVID-19. *Cancer Sci* 2020; **111:** 3379–85.

107 Brasen CL, Christensen H, Olsen DA, et al. Daily monitoring of viral load measured as SARS-CoV-2 antigen and RNA in blood, IL-6, CRP and complement C3d predicts outcome in patients hospitalized with COVID-19. *Clin Chem Lab Med* 2021; **59:** 1988–97.

108 Bury L, Camilloni B, Castronari R, et al. Search for SARS-CoV-2 RNA in platelets from COVID-19 patients. *Platelets* 2021; **32:** 284–87.

109 Colagrossi L, Antonello M, Renica S, et al. SARS-CoV-2 RNA in plasma samples of COVID-19 affected individuals: a cross-sectional proof-of-concept study. *BMC Infect Dis* 2021; **21:** 184.

110 Gutmann C, Takov K, Burnap SA, et al. SARS-CoV-2 RNAemia and proteomic trajectories inform prognostication in COVID-19 patients admitted to intensive care. *Nat Commun* 2021; **12:** 3406.

111 Hagman K, Hedenstierna M, Gille-Johnson P, et al. Severe acute respiratory syndrome coronavirus 2 RNA in serum as predictor of severe outcome in coronavirus disease 2019: a retrospective cohort study. *Clin Infect Dis* 2021; **73:** e2995–3001.

112 Hagman K, Hedenstierna M, Widaeus J, et al. Correlation of SARS-CoV-2 nasopharyngeal CT values with viremia and mortality in adults hospitalized with COVID-19. *Open Forum Infect Dis* 2022; **9:** ofac463.

113 Hasanoglu I, Korukluoglu G, Asilturk D, et al. Higher viral loads in asymptomatic COVID-19 patients might be the invisible part of the iceberg. *Infection* 2021; **49:** 117–26.

114 Heinrich F, Nentwich MF, Bibiza-Freiwald E, et al. SARS-CoV-2 blood RNA load predicts outcome in critically ill COVID-19 patients. *Open Forum Infect Dis* 2021; **8:** ofab509.

115 Hogan CA, Stevens BA, Sahoo MK, et al. High frequency of SARS-CoV-2 RNAemia and association with severe disease. *Clin Infect Dis* 2021; **72:** e291–95.

116 Järhult JD, Hultström M, Bergqvist A, Frithiof R, Lipcsey M. The impact of viremia on organ failure, biomarkers and mortality in a Swedish cohort of critically ill COVID-19 patients. *Sci Rep* 2021; **11:** 7163.

117 Maeda MFY, Brizot ML, Gibelli MABC, et al. Vertical transmission of SARS-CoV2 during pregnancy: a high-risk cohort. *Prenat Diagn* 2021; **41:** 998–1008.

118 Michot JM, Hueso T, Ibrahimi N, et al. Severe COVID-19 in patients with hematological cancers presenting with viremia. *Ann Oncol* 2021; **32:** 1297–300.

119 Miki S, Sasaki H, Horiuchi H, et al. On-admission SARS-CoV-2 RNAemia as a single potent predictive marker of critical condition development and mortality in COVID-19. *PLoS One* 2021; **16:** e0254640.

120 Omland T, Prebensen C, Jonassen C, et al. Soluble ST2 concentrations associate with in-hospital mortality and need for mechanical ventilation in unselected patients with COVID-19. *Open Heart* 2021; **8:** e001884.

121 Owusu M, Sylverken AA, El-Duah P, et al. Low risk of SARS-CoV-2 in blood transfusion. *PLoS One* 2021; **16:** e0249069.

122 Patterson BK, Seethamraju H, Dhody K, et al. CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and decreases SARS-CoV2 RNA in plasma by day 14. *Int J Infect Dis* 2021; **103:** 25–32.

123 Pinninti SG, Pati S, Poole C, et al. Virological characteristics of hospitalized children with SARS-CoV-2 infection. *Pediatrics* 2021; **147:** e2020037812.

124 Pourakbari B, Mahmoudi S, Mahmoudieh Y, et al. SARS-CoV-2 RNAaemia in children: an Iranian referral hospital-based study. *J Med Virol* 2021; **93:** 5452–57.

125 Prakash S, Shukla S, Mishra H, et al. SARS-CoV-2-RNA persists longer in faecal sample as compared to nasal and throat swab samples of COVID-19 patients'; an observational study. *Indian J Med Microbiol* 2021; **39:** 122–24.

126 Prebensen C, Myhre PL, Jonassen C, et al. Severe acute respiratory syndrome coronavirus 2 RNA in plasma is associated with intensive care unit admission and mortality in patients hospitalized with coronavirus disease 2019. *Clin Infect Dis* 2021; **73:** e799–802.

127 Richter E, Al Arashi D, Schulte B, et al. Detectable SARS-CoV-2 RNAemia in critically ill patients, but not in mild and asymptomatic infections. *Transfus Med Hemother* 2021; **48:** 154–60.

128 Rodríguez-Serrano DA, Roy-Vallejo E, Zurita Cruz ND, et al. Detection of SARS-CoV-2 RNA in serum is associated with increased mortality risk in hospitalized COVID-19 patients. *Sci Rep* 2021; **11:** 13134.

129 Roedl K, Jarczak D, Drolz A, et al. Severe liver dysfunction complicating course of COVID-19 in the critically ill: multifactorial cause or direct viral effect? *Ann Intensive Care* 2021; **11:** 44.

130 Sharma K, Aggarwala P, Gandhi D, et al. Comparative analysis of various clinical specimens in detection of SARS-CoV-2 using rRT-PCR in new and follow up cases of COVID-19 infection: quest for the best choice. *PLoS One* 2021; **16:** e0249408.

131 Siddiqi HK, Weber B, Zhou G, et al. Increased prevalence of myocardial injury in patients with SARS-CoV-2 viremia. *Am J Med* 2021; **134:** 542–46.

132 Smith N, Goncalves P, Charbit B, et al. Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection. *Nat Immunol* 2021; **22:** 1428–39.

133 Strasser EF, Steininger PA, Korn K, et al. Validation of a SARS-CoV-2 RNA RT-PCR assay for high-throughput testing in blood of COVID-19 convalescent plasma donors and patients. *Transfusion* 2021; **61:** 368–74.

134 Tedim AP, Almansa R, Domínguez-Gil M, et al. Comparison of real-time and droplet digital PCR to detect and quantify SARS-CoV-2 RNA in plasma. *Eur J Clin Invest* 2021; **51:** e13501.

135 Trombetta AC, Farias GB, Gomes AMC, et al. Severe COVID-19 recovery is associated with timely acquisition of a myeloid cell immune-regulatory phenotype. *Front Immunol* 2021; **12:** 691725.

136 Van Cleemput J, van Snippenberg W, Lambrechts L, et al. Organ-specific genome diversity of replication-competent SARS-CoV-2. *Nat Commun* 2021; **12:** 6612.

137 van Riel D, Embregts CWE, Sips GJ, et al. Temporal kinetics of RNAemia and associated systemic cytokines in hospitalized COVID-19 patients. *mSphere* 2021; **6:** e0031121.

138 Veyer D, Kernéis S, Poulet G, et al. Highly sensitive quantification of plasma severe acute respiratory syndrome coronavirus 2 RNA sheds light on its potential clinical value. *Clin Infect Dis* 2021; **73:** e2890?97.

139 Wirz OF, Röltgen K, Stevens BA, et al. Use of outpatient-derived COVID-19 convalescent plasma in COVID-19 patients before seroconversion. *Front Immunol* 2021; **12:** 739037.

140 Zhang R, Wang H, Tian S, Deng J. Adenovirus viremia may predict adenovirus pneumonia severity in immunocompetent children. *BMC Infect Dis* 2021; **21:** 213.

141 Zhang W, Liu W, Lin J, et al. Highly prevalent SARS-CoV-2 antigenemia in COVID-19 patients. *Infect Dis Immun* 2022; **2:** 193–99.

142 Ahava MJ, Kurkela S, Kuivanen S, Lappalainen M, Jarva H, Jääskeläinen AJ. Detection of SARS-CoV-2 nucleocapsid antigen from serum can aid in timing of COVID-19 infection. *J Virol Methods* 2022; **302:** 114469.

143 Anjos D, Fiaccadori FS, Servian CDP, et al. SARS-CoV-2 loads in urine, sera and stool specimens in association with clinical features of COVID-19 patients. *J Clin Virol Plus* 2022; **2:** 100059.

144 Bruneau T, Wack M, Poulet G, et al. Circulating ubiquitous RNA, a highly predictive and prognostic biomarker in hospitalized coronavirus disease 2019 (COVID-19) patients. *Clin Infect Dis* 2022; **75:** e410–17.

145 Cardeñoso Domingo L, Roy Vallejo E, Zurita Cruz ND, et al. Relevant SARS-CoV-2 viremia is associated with COVID-19 severity: prospective cohort study and validation cohort. *J Med Virol* 2022; **94:** 5260–70.

146 Costa R, Alberola J, Olea B, et al. Combined kinetic analysis of SARS-CoV-2 RNAemia, N-antigenemia and virus-specific antibodies in critically ill adult COVID-19 patients. *Sci Rep* 2022; **12:** 8273.

147 Hanson BA, Visvabharathy L, Ali ST, et al. Plasma biomarkers of neuropathogenesis in hospitalized patients with COVID-19 and those with postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm* 2022; **9:** e1151.

148 Jacobs JL, Bain W, Naqvi A, et al. Severe acute respiratory syndrome coronavirus 2 viremia is associated with coronavirus disease 2019 severity and predicts clinical outcomes. *Clin Infect Dis* 2022; **74:** 1525–33.

149 Kawasuji H, Morinaga Y, Tani H, et al. SARS-CoV-2 RNAemia with a higher nasopharyngeal viral load is strongly associated with disease severity and mortality in patients with COVID-19. *J Med Virol* 2022; **94:** 147–53.

150 Marconato M, Abela IA, Hauser A, et al. Antibodies from convalescent plasma promote SARS-CoV-2 clearance in individuals with and without endogenous antibody response. *J Clin Invest* 2022; **132:** e158190.

151 Martin-Vicente M, Almansa R, Martínez I, et al. Low anti-SARS-CoV-2 S antibody levels predict increased mortality and dissemination of viral components in the blood of critical COVID-19 patients. *J Intern Med* 2022; **291:** 232–40.

152 Martín Ramírez A, Zurita Cruz ND, Gutiérrez-Cobos A, et al. Evaluation of two RT-PCR techniques for SARS-CoV-2 RNA detection in serum for microbiological diagnosis. *J Virol Methods* 2022; **300:** 114411.

153 Mertz C, Glowinski R, Cohen SH, et al. Severe acute respiratory syndrome coronavirus 2 RNAemia and clinical outcomes in children with coronavirus disease 2019. *J Infect Dis* 2022; **225:** 208–13.

154 Mithal LB, Otero S, Simons LM, et al. Low-level SARS-CoV-2 viremia coincident with COVID placentitis and stillbirth. *Placenta* 2022; **121:** 79–81.

155 Monchi M, Bruneau T, Jochmans S, et al. Association of high SARS-CoV-2 RNAemia with diabetes and mortality in critically ill COVID-19 patients. *iScience* 2022; **25:** 104075.

156 Nagaoka K, Kawasuji H, Murai Y, et al. Circulating type I interferon levels in the early phase of COVID-19 are associated with the development of respiratory failure. *Front Immunol* 2022; **13:** 844304.

157 Nagaoka K, Kawasuji H, Takegoshi Y, et al. Predictive values of immune indicators on respiratory failure in the early phase of COVID-19 due to Delta and precedent variants. *Front Immunol* 2023; **14:** 1197436.

158 Nagaoka K, Kawasuji H, Takegoshi Y, et al. Association of Subpleural ground-glass opacities with respiratory failure and RNAemia in COVID-19. *Eur Radiol* 2023; **33:** 4713–22.

159 Olea B, Albert E, Torres I, et al. SARS-CoV-2 N-antigenemia in critically ill adult COVID-19 patients: frequency and association with inflammatory and tissue-damage biomarkers. *J Med Virol* 2022; **94:** 222–28.

160 Ram-Mohan N, Kim D, Rogers AJ, et al. Association between SARS-CoV-2 RNAemia and postacute sequelae of COVID-19. *Open Forum Infect Dis* 2021; **9:** ofab646.

161 Ram-Mohan N, Kim D, Zudock EJ, et al. SARS-CoV-2 RNAemia predicts clinical deterioration and extrapulmonary complications from COVID-19. *Clin Infect Dis* 2022; **74:** 218–26.

162 Rosas IO, Bräu N, Waters M, et al. Tocilizumab in patients hospitalised with COVID-19 pneumonia: efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). *EClinicalMedicine* 2022; **47:** 101409.

163 Rovito R, Bono V, Augello M, et al. Association between SARS-CoV-2 RNAemia and dysregulated immune response in acutely ill hospitalized COVID-19 patients. *Sci Rep* 2022; **12:** 19658.

164 Sigal GB, Novak T, Mathew A, et al. Measurement of severe acute respiratory syndrome coronavirus 2 antigens in plasma of pediatric patients with acute coronavirus disease 2019 or multisystem inflammatory syndrome in children using an ultrasensitive and quantitative immunoassay. *Clin Infect Dis* 2022; **75:** 1351–58.

165 Solis M, Gallais F, Garnier-Kepka S, et al. Combining predictive markers for severe COVID-19: torquetenovirus DNA load and SARS-CoV-2 RNAemia. *J Clin Virol* 2022; **148:** 105120.

166 Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022; **185:** 881–95.e20.

167 Verkerke HP, Damhorst GL, Graciaa DS, et al. Nucleocapsid antigenemia is a marker of acute SARS-CoV-2 infection. *J Infect Dis* 2022; **226:** 1577–87.

168 Vigil-Vázquez S, Carrasco-García I, Hernanz-Lobo A, et al. Impact of gestational COVID-19 on neonatal outcomes: is vertical infection possible? *Pediatr Infect Dis J* 2022; **41:** 466–72.

169 Zou X, Mu S, Wang Y, et al. Characterization of two SARS-CoV-2 subgenomic RNA dynamics in severe COVID-19 patients. *Virol Sin* 2022; **37:** 30–37.

170 Zurita-Cruz ND, Martín-Ramírez A, Rodríguez-Serrano DA, et al. Usefulness of real-time RT-PCR to understand the kinetics of SARS-CoV-2 in blood: a prospective study. *J Clin Virol* 2022; **152:** 105166.

171 Bauer C, Mack E, Hefter V, et al. Impaired systemic nucleocapsid antigen clearance in severe COVID-19. *J Med Virol* 2023; **95:** e29032.

172 Bauer RN, Teterina A, Shivram H, et al. Prognostic value of severe acute respiratory syndrome coronavirus-2 viral load and antibodies in patients hospitalized with COVID-19. *Clin Transl Sci* 2023; **16:** 1049–62.

173 Chenane HR, Lingas G, Menidjel R, et al. High sera levels of SARS-CoV-2 N antigen are associated with death in hospitalized COVID-19 patients. *J Med Virol* 2023; **95:** e29247.

174 Cizmic A, Eichel VM, Weidner NM, et al. Viral load of SARS-CoV-2 in surgical smoke in minimally invasive and open surgery: a single-center prospective clinical trial. *Sci Rep* 2023; **13:** 20299.

175 Damhorst GL, Verkerke HP, Harrington KRV, et al. SARS-CoV-2 antigenemia is associated with pneumonia in children but lacks sensitivity to diagnose acute infection. *Pediatr Infect Dis J* 2023; **42:** 130–35.

176 Damhorst GL, Schoof N, Nguyen PV, et al. Investigation of blood plasma viral nucleocapsid antigen as a marker of active severe acute respiratory syndrome coronavirus 2 omicron variant infection. *Open Forum Infect Dis* 2023; **10:** ofad226.

177 Giacomelli A, Righini E, Micheli V, et al. SARS-CoV-2 viremia and COVID-19 mortality: a prospective observational study. *PLoS One* 2023; **18:** e0281052.

178 Hijano DR, Ferrolino JA, Hidinger J, et al. Clinical correlation of adenoviral load in the respiratory tract measured by digital PCR in immunocompromised children. *Open Forum Infect Dis* 2023; **10:** ofad030.

179 Jamalidoust M, Hamzavi SS, Shorafa E, Namayandeh M, Batool L, Abootalebi SN. Comparing clinical presentation, viremia, and immunological factors at various severity presentations in hospitalized children affected by COVID-19: a cross-sectional study. *Health Sci Rep* 2023; **6:** e1259.

180 Joly C, Desjardins D, Porcher R, et al. More rapid blood interferon α2 decline in fatal versus surviving COVID-19 patients. *Front Immunol* 2023; **14:** 1250214.

181 Krifors A, Karlsson L, Ekman M, Lorant C, Skorup P. The kinetics of SARS-CoV-2 viremia in COVID-19 patients receiving remdesivir. *Eur J Clin Microbiol Infect Dis* 2023; **42:** 951–58.

182 Mendes-Correa MC, Salomão MC, Ghilardi F, et al. SARS-CoV-2 detection and culture in different biological specimens from immunocompetent and immunosuppressed COVID-19 patients infected with two different viral strains. *Viruses* 2023; **15:** 1270.

183 Piqué B, Peña K, Riu F, et al. SARS-CoV-2 serum viral load and prognostic markers proposal for COVID-19 pneumonia in low-dose radiation therapy treated patients. *J Clin Med* 2023; **12:** 798.

184 Rombauts A, Infante C, de Lagos MDÁM, et al. Impact of SARS-CoV-2 RNAemia and other risk factors on long-COVID: a prospective observational multicentre cohort study. *J Infect* 2023; **86:** 154–225.

185 Roy-Vallejo E, Fernández De Córdoba-Oñate S, Delgado-Wicke P, et al. Occurrence of SARS-CoV-2 viremia is associated with genetic variants of genes related to COVID-19 pathogenesis. *Front Med* 2023; **10:** 1215246.

186 Salto-Alejandre S, Carretero-Ledesma M, Camacho-Martínez P, et al. Serum IFN-γ and RNAemia temporal profiles as biomarkers of severe COVID-19 in solid organ transplant and immunocompetent patients. *J Infect* 2023; **86:** 529–33.

187 Tanaka H, Namkoong H, Chubachi S, et al. Clinical characteristics of patients with COVID-19 harboring detectable intracellular SARS-CoV-2 RNA in peripheral blood cells. *Int J Infect Dis* 2023; **135:** 41–44.

188 Vecchio J, Regan J, Jiang Y, et al. Viral and immunologic evaluation of smokers with severe COVID-19. *Sci Rep* 2023; **13:** 17898.

189 Wei J, Zang N, Zhang J, et al. Genome and proteomic analysis of risk factors for fatal outcome in children with severe community-acquired pneumonia caused by human adenovirus 7. *J Med Virol* 2023; **95:** e29182.

190 Augello M, Bono V, Rovito R, et al. Association between SARS-CoV-2 RNAemia, skewed T cell responses, inflammation, and severity in hospitalized COVID-19 people living with HIV. *iScience* 2023; **27:** 108673.

191 Capelli N, Domitien Payet L, Alcocer Cordellat C, et al. SARS-CoV-2 nucleocapsid antigen in plasma of children hospitalized for COVID-19 or with incidental detection of SARS-CoV-2 infection. *J Med Virol* 2024; **96:** e29358.

192 de la Fuente A, Postigo T, Sanus Ferri F, et al. Synergistic impact of N-antigenemia profiled by a rapid antigen test and low anti-S1 antibodies on the risk of hospitalization in COVID-19. *Int J Infect Dis* 2024; **140:** 132–35.

193 Favresse J, Bayart JL, David C, et al. Serum SARS-CoV-2 antigens for the determination of COVID-19 severity. *Viruses* 2022; **14:** 1653.

194 Nomoto H, Kutsuna S, Okuma K, et al. No SARS-CoV-2 RNA detected in the convalescent plasma of COVID-19 patients with different disease severity. *J Infect Chemother* 2021; **27:** 653–55.

195 Regan J, Flynn JP, Rosenthal A, et al. Viral load kinetics of severe acute respiratory syndrome coronavirus 2 in hospitalized individuals with coronavirus disease 2019. *Open Forum Infect Dis* 2021; **8:** ofab153.

196 Graciaa DS, Verkerke HP, Guarner J, et al. Estimating severe acute respiratory coronavirus virus 2 (SARS-CoV-2) seroprevalence from residual clinical blood samples, January–March 2021. *Antimicrob Steward Healthc Epidemiol* 2022; **2:** e159.

197 Chatterjee S, Datey A, Sengupta S, et al. Clinical, virological, immunological, and genomic characterization of asymptomatic and symptomatic cases with SARS-CoV-2 infection in India. *Front Cell Infect Microbiol* 2021; **11:** 725035.

198 Hagman K, Hedenstierna M, Rudling J, et al. Duration of SARS-CoV-2 viremia and its correlation to mortality and inflammatory parameters in patients hospitalized for COVID-19: a cohort study. *Diagn Microbiol Infect Dis* 2022; **102:** 115595.

199 Saji R, Nishii M, Sakai K, et al. Combining IL-6 and SARS-CoV-2 RNAaemia-based risk stratification for fatal outcomes of COVID-19. *PLoS One* 2021; **16:** e0256022.

200 Perkins DJ, Yingling AV, Cheng Q, et al. Elevated SARS-CoV-2 in peripheral blood and increased COVID-19 severity in American Indians/Alaska Natives. *Exp Biol Med (Maywood)* 2022; **247:** 1253–63.

201 Lawrence Panchali MJ, Kim CM, Seo JW, Kim DY, Yun NR, Kim DM. SARS-CoV-2 RNAemia and disease severity in COVID-19 patients. *Viruses* 2023; **15:** 1560.

202 Brunet-Ratnasingham E, Morin S, Randolph HE, et al. Sustained IFN signaling is associated with delayed development of SARS-CoV-2-specific immunity. *Nat Commun* 2024; **15:** 4177.

203 Destremau M, Chaussade H, Hemar V, et al. Convalescent plasma transfusion for immunocompromised viremic patients with COVID-19: a retrospective multicenter study. *J Med Virol* 2024; **96:** e29603.

204 Courties A, Boussier J, Hadjadj J, et al. Regulation of the acetylcholine/α7nAChR anti-inflammatory pathway in COVID-19 patients. *Sci Rep* 2021; **11:** 11886.

205 Kuri-Ayache M, Rivera-Cavazos A, Pérez-Castillo MF, et al. Viral load and its relationship with the inflammatory response and clinical outcomes in hospitalization of patients with COVID-19. *Front Immunol* 2023; **13:** 1060840.

206 Wargodsky R, Dela Cruz P, LaFleur J, et al. RNA sequencing in COVID-19 patients identifies neutrophil activation biomarkers as a promising diagnostic platform for infections. *PLoS One* 2022; **17:** e0261679.

207 Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004; **31:** 304–09.

208 Lee N, Chan PK, Wong CK, et al. Viral clearance and inflammatory response patterns in adults hospitalized for pandemic 2009 influenza A(H1N1) virus pneumonia. *Antivir Ther* 2011; **16:** 237–47.

209 Swank Z, Senussi Y, Manickas-Hill Z, et al. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. *Clin Infect Dis* 2023; **76:** e487–90.

210 Schultheiß C, Willscher E, Paschold L, et al. Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19. *J Med Virol* 2023; **95:** e28364.

211 Tejerina F, Catalan P, Rodriguez-Grande C, et al, Post-COVID-19 syndrome. SARS-CoV-2 RNA detection in plasma, stool, and urine in patients with persistent symptoms after COVID-19. *BMC Infect Dis* 2022; **22:** 211.

212 Sun X, Gao C, Zhao K, et al. Immune-profiling of SARS-CoV-2 viremic patients reveals dysregulated innate immune responses. *Front Immunol* 2022; **13:** 984553.

213 Corley MJ, Pang APS, Dody K, et al. Genome-wide DNA methylation profiling of peripheral blood reveals an epigenetic signature associated with severe COVID-19. *J Leukoc Biol* 2021; **110:** 21–26.

214 Shen XR, Geng R, Li Q, et al. ACE2-independent infection of T lymphocytes by SARS-CoV-2. *Signal Transduct Target Ther* 2022; **7:** 83.

215 Roy-Vallejo E, Cardeñoso L, Triguero-Martínez A, et al. SARS-CoV-2 viremia precedes an IL6 response in severe COVID-19 patients: results of a longitudinal prospective cohort. *Front Med* 2022; **9:** 855639.

216 Wick KD, Siegel L, Neaton JD, et al. RAGE has potential pathogenetic and prognostic value in nonintubated hospitalized patients with COVID-19. *JCI Insight* 2022; **7:** e157499.

217 Stein SR, Ramelli SC, Grazioli A, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* 2022; **612:** 758–63.

218 Carrau L, Frere JJ, Golynker I, et al. Delayed engagement of host defenses enables SARS-CoV-2 viremia and productive infection of distal organs in the hamster model of COVID-19. *Sci Signal* 2023; **16:** eadg5470.

219 Zhang Y, Bharathi V, Dokoshi T, et al. Viral afterlife: SARS-CoV-2 as a reservoir of immunomimetic peptides that reassemble into proinflammatory supramolecular complexes. *Proc Natl Acad Sci U S A* 2024; **121:** e2300644120.

220 Wang X, Tan J, Zhao J, Ye Z, Hewlett I. Highly pathogenic avian influenza A virus (H5N1) can be transmitted in ferrets by transfusion. *BMC Infect Dis* 2014; **14:** 192.

221 Wu XX, Tang SJ, Yao SH, et al. The viral distribution and pathological characteristics of BALB/c mice infected with highly pathogenic influenza H7N9 virus. *Virol J* 2021; **18:** 237.