RT-PCR at the time of admission. The authors presented the clinical management protocol for all patients admitted to the emergency room with respiratory failure and/or fever who required management for suspected COVID-19. The findings are in line with the outcomes of our study, as 50.3% of patients admitted to the hospital in our cohort did not have a single positive RT-PCR swab result. Likewise, the diagnostic and treatment strategies were based primarily on clinical and laboratory findings for all admitted patients, irrespective of the RT-PCR results.

A high false-negative rate of the RT-PCR tests, varying between 20% and 66% depending on the day since symptom onset, has been previously reported [2]. Although negative RT-PCR tests were found in almost half of patients in a few large cohort studies [3–5], including our own, patients with suspected COVID-19 infection were normally excluded from statistical analysis in the absence of the positive test result [3, 4, 6–9]. We would like to emphasize that most of the national and international data on COVID-19 cases and deaths are based exclusively on positive RT-PCR and may seriously underestimate the true prevalence and mortality of COVID-19. There is a pressing need to account for the number of patients with clinical features of COVID-19 and negative RT-PCR.

Russo et al suggest that some clinical and laboratory features may help physicians discriminate cases of SARS-CoV-2 from other causes, regardless of the RT-PCR results. We support authors in their initiative to develop reliable parameter sets to allow for early differentiation of patients at higher risk of unfavorable outcomes. This is very much in line with the national and international efforts to harmonize and collate data on clinical characteristics of COVID-19 and develop clinical algorithms and scoring systems. A recent multicenter study from the International Severe Acute Respiratory and Emerging Infections Consortium Coronavirus Clinical Characterisation Consortium resulted in the development of a very promising pragmatic risk score to predict mortality in patients admitted to the hospital with COVID-19 [10], demonstrating an excellent negative predictive value. Future research should focus on the development and validation of reliable and user-friendly tools for use in routine clinical practice.

Notes

Financial support. We thank Russian Foundation for Basic Research (RFBR) (grant 20-04-60063) for supporting the work.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Daniel Munblit,[1,2,3] Nikita A. Nekliudov,[1] Polina Bugaeva,[1] Oleg Blyuss,[1,4] Peter Timashev,[5,6,7] John O. Warner,[2] Pasquale Comberiati,[8] Christian Apfelbacher,[9] Mikhail E. Politov,[10] Andrey Yavorovskiy,[10] Sergey Avdeev,[11] Valentina A. Kapustina,[12] Victor Fomin,[13] Andrey A. Svistunov,[13] Denis Butnaru,[13] and Petr Glybochko[13]

[1]Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child's Health, Sechenov First Moscow State Medical University, Moscow, Russia; [2]Inflammation, Repair and Development Section, National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London, United Kingdom; [3]Research and Clinical Center for Neuropsychiatry, Moscow, Russia; [4]School of Physics, Astronomy and Mathematics, University of Hertfordshire, College Lane, Hatfield, United Kingdom; [5]Institute for Regenerative Medicine, Sechenov First Moscow State Medical University, Moscow, Russia; [6]Chemistry Department, Lomonosov Moscow State University, Moscow, Russia; [7]Department of Polymers and Composites, N.N. Semenov Institute of Chemical Physics, Moscow, Russia; [8]Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, Pisa, Italy; [9]Institute of Social Medicine and Health Systems Research, Faculty of Medicine, Otto von Guericke University Magdeburg, Magdeburg, Germany; [10]Department of Intensive Care, Sechenov First Moscow State Medical University, Moscow, Russia; [11]Clinic of Pulmonology, Sechenov First Moscow State Medical University, Moscow, Russia; [12]Department of Internal Medicine No.1, Institute of Clinical Medicine, Sechenov First Moscow State Medical University, Moscow, Russia; and [13]Sechenov First Moscow State Medical University, Moscow, Russia

References

1. Russo A, Bellelli V, Ceccarelli G, et al. Comparison between hospitalized patients affected or not by COVID-19 (RESILIENCY study). Clin Infect Dis **2020**.
2. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Ann Intern Med **2020**; 173:262–7.
3. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series BMJ **2020**; 369:m1996.
4. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ **2020**; 369:m1966.
5. Munblit D, Nekliudov NA, Bugaeva P, et al. StopCOVID cohort: an observational study of 3,480 patients admitted to the Sechenov University hospital network in Moscow city for suspected COVID-19 infection. Clin Infect Dis **2020**.
6. Docherty AB, Harrison EM, Green CA, et al.; ISARIC4C Investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ **2020**; 369:m1985.
7. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with sars-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA **2020**; 323:1574–81.
8. Richardson S, Hirsch JS, Narasimhan M, et al.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA **2020**; 323:2052–9.
9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395:1054–62.
10. Knight SR, Ho A, Pius R, et al.; ISARIC4C Investigators. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C mortality score. BMJ **2020**; 370:m3339.

Correspondence: Daniel Munblit, Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child's Health, Sechenov First Moscow State Medical University (Sechenov University), 29, Shmitovskiy proezd, Moscow 123337, Russian Federation (daniel.munblit08@imperial.ac.uk).

Clinical Infectious Diseases® 2021;72(12):e1159–60

DOI: 10.1093/cid/ciaa1746

Clinical Disease Severity Scores and Viral Loads in Children With Respiratory Syncytial Virus Infection

To the Editor—We read with interest the article by Haddadin et al in this issue of *Clinical Infectious Diseases* [1]. As part of a prospective surveillance study, the authors enrolled a cohort of 898 children aged <5 years who presented with fever and/or respiratory symptoms to the emergency department or were hospitalized. Of those, 191 children had confirmed respiratory syncytial virus (RSV) infection, with a median age of 10 months (4.1–21); 34% had underlying

Table 1. Demographic, Clinical, and Virologic Parameters in Children With Respiratory Syncytial Virus Infection

Characteristic	Mild (CDSS 0–5) n = 308	Moderate (CDSS 6–9) n = 164	Severe (CDSS 10–15) n = 62	*P* Value
Demographics				
Age, months	3.4 (1.60–7.79)	3.4 (1.75–7.72)	2.2 (1.28–5.09)	**.009**
Age group, months				.07
<6	209 (68)	113 (69)	53 (86)	
6 to <12m	62 (20)	32 (19)	7 (11)	
12 to <24	38 (12)	19 (12)	2 (3)	
Sex, male	170 (55.2)	79 (48.2)	36 (58.1)	.25
Race				.86
White	190 (61.7)	109 (66.5)	40 (64.5)	
Black	70 (22.7)	31 (18.9)	12 (19.4)	
Other	48 (15.6)	24 (14.6)	10 (16.1)	
Vaginal delivery	209/295 (70.8)	108/159 (67.9)	49/61 (80.3)	.19
Breastfed	163/293 (55.6)	60/139 (43.2)	24/57 (42.1)	**.02**
Daycare attendance	85/294 (28.9)	40/139 (28.8)	14/57 (24.6)	.79
Smoke exposure	96/295 (32.5)	54/139 (38.8)	20/57 (35.1)	.43
Immunizations	261/301 (86.7)	141/162 (87.0)	54/62 (87.1)	.99
Asthma (family history)	142/308 (46.1)	77/164 (47.0)	36/62 (58.1)	.22
Clinical parameters				
Days of symptoms[a]	4.0 (3.0–6.0)	4.0 (3.0–5.0)	4.5 (3.0–6.0)	.35
Status				**<.001**
Inpatient	190 (61.7)	152 (92.7)	62 (100)	
Outpatient	118 (38.3)	12 (7.3)	0 (0)	
Length of stay, days	1.90 (1.20–2.82)	2.60 (1.70–3.80)	4.10 (3.30–7.32)	**<.001**
Viral load data				
RSV type				.72
A	159 (52)	91 (56)	32 (52)	
B	148 (48)	73 (44)	30 (48)	
RSV loads, $\log_{10}$ copies/mL	7.73 (6.91–8.32)	7.41 (6.69–8.09)	7.18 (6.09–7.87)	**<.001**

Abbreviations: CDSS, clinical disease severity score; RSV, respiratory syncytial virus.
[a]Duration of illness at study enrollment. Categorical data are expressed as frequencies (%) and analyzed using the Fisher or χ^2 test. Continuous data are expressed as median (25%–75% interquartile range) and analyzed using the Kruskal-Wallis with Dunn test to adjust for multiple comparisons. Values in bold indicate significant 2-sided *P* values.

medical conditions, and 79% of cases were caused by RSV A. The investigators found that in addition to younger age, a clinical disease severity score (CDSS), previously published by Garcia-Mauriño et al [2], was the more consistent parameter associated with severe disease, with an area under the curve of 0.849 (95% confidence interval, .629–.977; $P < .001$), while semiquantitative viral loads (cycle threshold values) were narrowly associated with severity. The study emphasizes the burden of RSV infection in older children, the value of clinical tools to assess disease severity, and the importance of combining detailed clinical and virologic data to unravel the factors that contribute to severe disease in these children.

We have extensively applied the CDSS used by Haddadin et al in our previous studies to assess disease severity in young infants with RSV infection [2–8]. The original CDSS was developed by Tal et al [9], which we modified to capture lung auscultation in a broader perspective, as wheezing is frequently absent in younger infants, and to also include the ability of the infant to feed, a parameter that is missing from previous scores but critical when evaluating infants and deciding the need for hospitalization.

Using the aforementioned score (RSV-CDSS), we recently analyzed the role of quantitative RSV loads in a large cohort of previously healthy children aged <2 years (90% <12 months) prospectively enrolled in the outpatient setting (n = 130) or hospitalized with moderate to severe disease (n = 404; Table 1). In this cohort, we found that viral loads were higher in infants with mild disease (ie, lower CDSS). Importantly, using polynomial and restricted cubic spline regression, we found that the association between age and RSV loads was roughly linear and differed according to age [6]. There was a decline in viral loads with increasing age among RSV inpatients and little association between age and viral loads in RSV outpatients.

The complex relationships between age, RSV loads, and disease severity may explain the differences observed between the Haddadin cohort and the cohort analyzed in our study, as the median age of

infants with severe disease in our cohort was significantly lower (2.2 months [1.3–5.1]) and children with chronic medical conditions were excluded.

Taken together, these studies emphasize the great burden of RSV in infants and young children, the value of the RSV-CDSS to assess disease severity across different ages, and the importance of age not only in terms of severity but on RSV loads. Further studies that include prospective longitudinal cohorts to further assess the value of the CDSS; the interactions between age, viral loads and severity; and whether they correlate with long-term outcomes are warranted.

Notes

Acknowledgments. We thank all members of the clinical research team at Nationwide Children's Hospital (NCH) for their extraordinary efforts to help enroll our patients and especially our patients and their families for their participation in the study.

Financial support. This work was supported in part by the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (grant AI112524), Janssen, and with intramural funds at NCH.

Disclaimer. The funding agencies had no input in data analyses and interpretation of study findings.

Potential conflicts of interest. A. M. and O. R. have received research grants from Janssen. A. M. has received fees for participation on advisory boards from Janssen, Roche, Sanofi, and Merck and grants from NIH. O. R. has received fees for participation on advisory boards from Sanofi/MedImmune, Merck, and Pfizer and fees for lectures from Pfizer and Merck; those fees were not related to the research described in this letter. O. R. has received grants to the institution from the Bill & Melinda Gates Foundation, Ohio Children's Hospital Association, and NIH outside the submitted work. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Asuncion Mejias,[1,2,3] Helena Brenes-Chacon,[1] Cristina Garcia-Mauriño,[1] Melissa Moore-Clingenpeel,[4] and Octavio Ramilo[1,2]

[1]Center for Vaccines and Immunity Abigail Wexner Research Institute, Department of Pediatrics at Nationwide Children's Hospital, Columbus, OH, USA, [2]Division of nfectious Diseases, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University College of Medicine; Columbus, OH, USA, [3]Departamento de Farmacologia y Pediatria, Facultad de Medicina, Universidad de Malaga, Malaga, Spain, and [4]Biostatistics Core, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA

Correspondence: Asuncion Mejias, Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205 (Asuncion.Mejias@nationwidechildrens.org)

References

1. Haddadin Z, Beveridge S, Fernandez K, et al. Respiratory syncytial virus disease severity in young children. Clin Infect Dis **2020**.
2. Garcia-Mauriño C, Moore-Clingenpeel M, Thomas J, et al. Viral load dynamics and clinical disease severity in infants with respiratory syncytial virus infection. J Infect Dis **2019**; 219:1207–15.
3. Mejias A, Dimo B, Suarez NM, et al. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. PLoS Med **2013**; 10:e1001549.
4. Mella C, Suarez-Arrabal MC, Lopez S, et al. Innate immune dysfunction is associated with enhanced disease severity in infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis **2013**; 207:564–73.
5. Suárez-Arrabal MC, Mella C, Lopez SM, et al. Nasopharyngeal bacterial burden and antibiotics: influence on inflammatory markers and disease severity in infants with respiratory syncytial virus bronchiolitis. J Infect **2015**; 71:458–69.
6. Brenes-Chacon H, Garcia-Mauriño C, Moore-Clingenpeel M, et al. Age-dependent interactions among clinical characteristics, viral loads and disease severity in young children with respiratory syncytial virus infection. Pediatr Infect Dis J **2020**. doi:10.1093/cid/ciaa1612
7. García C, Soriano-Fallas A, Lozano J, et al. Decreased innate immune cytokine responses correlate with disease severity in children with respiratory syncytial virus and human rhinovirus bronchiolitis. Pediatr Infect Dis J **2012**; 31:86–9.
8. Capella C, Chaiwatpongsakorn S, Gorrell E, et al. Prefusion F, postfusion F, G antibodies, and disease severity in infants and young children with acute respiratory syncytial virus infection. J Infect Dis **2017**; 216:1398–406.
9. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. Pediatrics **1983**; 71:13–8.

Correspondence: Asuncion Mejias, Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Division of Pediatric Infectious Diseases, The Ohio State University College of Medicine, Columbus, OH 43205 (Asuncion.Mejias@nationwidechildrens.org).

Clinical Infectious Diseases® 2021;72(12):e1160–2

DOI: 10.1093/cid/ciaa1752

Reply to Mejias et al

To the Editor—We read the letter by Mejias et al in response to our recent publication with appreciation [1, 2]. We agree that these collective studies continue to show that respiratory syncytial virus (RSV) is a leading cause of severe acute respiratory infections (ARIs) in young children and further reveal the complex interplay of host–virus factors in RSV disease severity.

Although children with prematurity and underlying medical conditions (UMCs) are at higher risk for severe RSV-ARI, most children hospitalized with RSV-ARI are previously healthy [3, 4]. While hospitalization is widely used as a marker of severity, admission decisions are based on the physician's discretion and can be affected by patient-related factors and parental preferences [4, 5]. Thus, we retrospectively calculated a clinical disease severity score (CDSS) based on the initial medical encounter for the child's current illness, including 48 hours before enrollment. The CDSS collectively incorporates several clinical signs and symptoms to reflect disease severity. Based on a priori–selected predictors of interest, we showed that the following variables were associated with higher odds of hospitalization:

1. Higher CDSS, underlining the role of disease severity in hospital admission, and further confirming the value of CDSS in assessing RSV disease severity.
2. Lower cycle threshold (Ct) values, indicating higher viral loads, highlighting the association of viral-related factors with severity.
3. Younger age and white race, reflecting the role of host-related factors in disease severity.

Further, our comparison of mean CDSS across a priori–selected predictors of interest allowed us to compare severity with less reliance on subjective factors that affect hospital admission, such as clinical decision making and provider/parent preferences. As mentioned by Mejias et al in their letter, Ct value has an inverse relationship with viral load, but it is not an actual viral load value. Nonetheless, we used Ct values as a continuous variable, showing that lower Ct values (indicating higher viral load) were associated with higher CDSS and hospitalization in RSV-positive children.