Effectiveness of three versus six feet of physical distancing for controlling spread of COVID-19 among primary and secondary students and staff: A retrospective, state-wide cohort study

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Summary: There is no significant difference in K-12 student and staff SARS-CoV-2 case rates in Massachusetts public school districts that implemented ≥3 feet versus ≥6 feet of physical distancing between students, provided other mitigation measures, such as universal masking, are implemented.

Abstract:

Background: National and international guidelines differ about the optimal physical distancing between students for prevention of SARS-CoV-2 transmission; studies directly comparing the impact of ≥3 versus ≥6 feet of physical distancing policies in school settings are lacking. Thus, our objective was to compare incident cases of SARS-CoV-2 in students and staff in Massachusetts public schools among districts with different physical distancing requirements. State guidance mandates masking for all school staff and for students in grades 2 and higher; the majority of districts required universal masking.

Methods: Community incidence rates of SARS-CoV-2, SARS-CoV-2 cases among students in grades K-12 and staff participating in-person learning, and district infection control plans were linked. Incidence rate ratios (IRR) for students and staff members in districts with ≥3 versus ≥6 feet of physical distancing were estimated using log-binomial regression; models adjusted for community incidence are also reported.

Results: Among 251 eligible school districts, 537,336 students and 99,390 staff attended in-person instruction during the 16-week study period, representing 6,400,175 student learning weeks and 1,342,574 staff learning weeks. Student case rates were similar in the 242 districts with ≥3 feet versus ≥6 feet of physical distancing between students (IRR, 0.891, 95% CI, 0.594-1.335); results were similar after adjusting for community incidence (adjusted IRR, 0.904, 95% CI, 0.616-1.325). Cases among school staff in districts with ≥3 feet versus ≥6 feet of physical distancing were also similar (IRR, 1.015, 95% CI, 0.754-1.365).

Conclusions: Lower physical distancing policies can be adopted in school settings with masking mandates without negatively impacting student or staff safety.

Key words: COVID-19, schools, physical distancing, infection control, adaptation

Background:

In March, 2020, as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) cases were increasing across the United States, schools across the country were closed, and the vast majority stayed closed for the remainder of the school year [1]. This policy decision was based on data adapted from influenza transmission, for which children and schools may be major drivers of pandemics [2]. Since schools were initially closed, new data have emerged suggesting that SARS-CoV-2 transmission in schools is limited, provided mitigation measures are implemented, and that children and schools are not the primary drivers of the pandemic [3–5].

Current guidance from the World Health Organization (WHO) is to maintain 1 meter (3.3 feet) between students while the Centers for Disease Control and Prevention (CDC) recommends students maintain 6 feet of distancing; the American Academy of Pediatrics recommends 3-6 feet [6–8]. However, the evidence for physical distancing to mitigate SARS-CoV-2 transmission in primary and secondary educational settings remains limited. Data from different countries that have implemented different physical distancing guidance in educational settings seem to suggest no major difference between ≥3 feet and ≥6 feet of distancing [9–12], though these studies did not directly compare different distancing requirements. To date, the impact of distancing in school settings has not been directly studied and remains a critical national policy question [13].

Between March and September of 2020, school officials designed plans for how to provide instruction for the 2020-2021 academic year. In June 2020, Massachusetts's Department of Elementary and Secondary Education (DESE) provided initial health and safety guidance for school re-opening to prioritize student return to school buildings in the fall [14]. Schools and districts were required to prepare and submit re-opening plans to the state that addressed district re-opening in three possible learning models (full in-person, hybrid, and remote) and addressed adherence to health and safety requirements including the use of masks/face coverings, physical distancing, grouping students into cohorts to minimize student interaction, utilizing symptom screening of staff and students, hand

hygiene, facilities cleaning, and dedicating isolation space for students displaying possible COVID-19 symptoms. Based on initial DESE guidance, students in grade 2 and above, and all staff were required to wear a mask/face covering in school buildings; districts were permitted to choose to require or recommend universal masking mandates for students in all grades. Schools were encouraged to aim for ≥6 feet of distancing between individuals when possible, with a minimum requirement of ≥3 feet of distancing between students [14].

In this retrospective analysis of data from public schools in the state of Massachusetts that opened with any in-person learning, we sought to measure the effectiveness of different physical distancing policies (≥3 versus ≥6 feet) on incidence of SARS-CoV-2 infections among students and school staff after school re-opening in fall 2020.

Methods

Data sources:

District Infection Control Plans

Publicly available district infection control plans, which were developed independently across the state but with guidance and ultimate approval from DESE, were identified through a variety of sources, including the Boston Globe school tracker [15] and public documents available on town websites. A standardized data extraction template was created using Microsoft Forms (Supplementary materials) and each district plan was individually reviewed and entered into the dataset. Variables of interest included school model type (e.g., fully remote, hybrid, or full in-person) and details of infection control strategies adopted by the district (e.g., physical distancing of ≥3 versus ≥6 feet, details of masking policy, including details about how the masking policy was applied to students in younger grades, ventilation upgrades, cleaning protocols).

Districts that permitted a minimum of ≥3 feet of distancing, even if greater distances were "preferred," were classified as allowing ≥3 feet of distancing between students. Similarly, districts that allowed ≥3 feet of distancing for some grades, even if not for all, were classified as permitting ≥3 feet of distancing. Districts that implemented intermediate

distancing requirements (e.g., minimum of 4 feet, 4.5 feet, 5 feet) were excluded from the primary analysis. Districts that allowed ≥3 feet of physical distancing in their full re-opening plan but opened in a hybrid learning model with requirements of ≥6 feet in the hybrid model, were classified as requiring ≥6 feet of physical distancing. Districts with contradictory recommendations (e.g., statements of permitting 3-6 feet in some sections of the infection control plan but requiring 6 feet in others) were excluded.

Prior to data abstraction, three investigators abstracted and entered the same infection control plans. After an inter-rater reliability score >80% was achieved for all variables (five districts reviewed, one round), data abstraction and entry was continued. To ensure data quality and accuracy of the physical distancing variable, all districts that included a minimum of ≥3 feet of distancing in their infection control plan underwent a double-check. If there was disagreement between the two reviews, then a third reviewer also manually reviewed the district plan and made a final decision regarding classification of the district policy. Additionally, a random sample of 10% of the districts classified as requiring ≥6 feet of physical distancing underwent a second review to ensure accuracy.

Case and Enrollment Data:

We obtained data on positive SARS-CoV-2 case counts from the DESE website, where they are available publicly, for the period of September 24, 2020 through January 27, 2021 [16]. District-level SARS-CoV-2 case counts are reported by school districts to DESE weekly.

Mandatory case reporting to DESE is only required for districts with any in-person learning (full in-person or hybrid districts). Case counts for students include students with a laboratory-confirmed diagnosis of SARS-CoV-2 infection who are enrolled in hybrid or in-person learning models and were in a school building within the seven days prior to the positive test. Similarly, staff case counts only include those who had been in a school building in the seven days prior to the laboratory confirmed positive test. Individual school districts are responsible for reporting these data to DESE.

Student enrollment data was provided electronically to the research team from DESE [17]. This includes total enrollment and counts of students enrolled in each learning model, in-person, hybrid, and remote, by district. DESE pulled this information from the district information system on a biweekly basis. The in-person, hybrid, and remote counts represent what the district is reporting at that time. In-person counts vary by week and are lower in the winter surge period, although detailed data about school closures is not reported.

Because in-person staff counts are not part of the dataset, we estimated these by using the 2018-2019 National Center for Education Statistics Common Core of Data (NCES CCD) statistics [18] for total full-time staff and teachers for all districts with at least 5% of enrolled students in an in-person or hybrid learning model. District demographic data (proportion of children aged 5-17 living in poverty, racial and ethnic enrollment within the school district) were also obtained from NCES CCD.

Community Case Data

Community incidence data was obtained from USAFacts [19], at the county level, dividing each county's totals among the county's zip codes, weighting by zip code population. These zip code-level community rates were matched to the district data using the zip code of the district's location in the NCES CCD dataset to provide a comparison for school rates and the surrounding community rates.

Analysis:

Because the number of students on-campus varies over the study period, we define high on-campus enrollment as districts with an average of 80% or more of their total enrolled students participating in on-campus instruction throughout the time period. Lower on-campus enrollment is defined as districts with an average of less than 80% of enrolled students participating in on-campus instruction.

After the three data sets were combined, we calculated the student and staff incidence rates for each district-week. We calculated the daily student incidence rate per

100,000 students who were attending in-person or hybrid models, and the daily staff incidence rate per 100,000 staff members for districts with at least 5% in-person or hybrid attendance. Weeks with less than 5% of total enrollment as in-person or hybrid attendance were excluded from the analysis.

To assess the impact of distancing policies on incidence of infection rates, we estimated negative binomial regression models. We used separate regression models for student and staff infection incidence outcomes. The key independent variable in these models was an indicator for a policy of 6 feet distance. We also estimated models controlling for community SARS-CoV-2 incidence and controlling for district demographic variables (proportion of children living in poverty, racial and ethnic enrollment within the district). In each model, standard errors were clustered by district and all models included week fixed effects to capture week-specific factors that were constant across districts. All data were analyzed using STATA and Microsoft Excel.

Sensitivity Analyses:

To ensure our findings were robust and not driven by other infection control mitigation measures, we conducted two sensitivity analyses. First, we re-estimated models after excluding districts with surveillance testing programs and re-estimated unadjusted and adjusted incidence rate ratios. We also estimated models among districts that permitted less than 6 feet of physical distancing (e.g., included districts that allowed 4-5 feet of distancing in the analysis).

Results:

Among 279 districts with detailed infection control plans available for review, 266 opened for any type of in-person learning during the period from September 24, 2020 to January 27, 2021 (hybrid and/or full-in person). Nine districts allowed intermediate distancing (e.g., 4-5 feet) and were excluded from the primary analysis. Two districts allowed 3 feet among some grades, but 6 feet among others (one allowing 3 feet for high school, another

allowing 3 feet for younger grade-levels). Two district's plans included contradictory statements regarding their physical distancing policy and were excluded. Districts that remained fully remote until November 1, 2020 were also excluded, leaving 251 districts in our analysis.

Within districts meeting inclusion criteria, 537,336 students and 99,390 staff were in attendance in school buildings, representing 6,400,175 student learning weeks and 1,342,574 staff learning weeks. During the entire study period, 4226 cases were reported in students and 2382 in school staff (daily incidence rate by week, Table 1). Because learning models vary by district over the study period, we instead consider on-campus enrollment by comparing the number of students enrolled in both in-person and hybrid models compared to total district enrollment. The majority of districts that opened for any in-person learning did so with lower on-campus enrollment, which we define as an average of less than 80% of enrolled students on campus during the study period (161/251, 64.14% lower on-campus enrollment; 90/251,35.86% high on-campus enrollment). 98.01% of districts included applied the same infection control policy, including distancing recommendations, across all grade levels. 100% of districts with any type of in-person learning adopted universal masking for both students in grade 2 and above and for school staff. 69.72% of districts required masking for younger grades, although the policy was not mandated by the state, and 26.29% of districts strongly encouraged masking for students in the younger grades. Three districts required masking for students in grade 1 and above and seven districts did not have details in their masking policy to comment on grade requirements. Other commonly implemented interventions included physical distancing between students (48 ≥3 foot requirement, 194, ≥6 foot requirement, 9, 4-5 foot requirement), cohorting of students (214/232, 92.24%), enhanced disinfection protocols (218/227, 96.04%) and variable ventilation interventions (205/227, 90.31%) (Table 2).

Districts that implemented ≥3 feet of distancing between students reported 895 cases among students and 431 cases among staff (Figure 1). Districts with ≥6 feet of physical distancing reported 3223 cases among students and 2382 among staff, (unadjusted

incidence rate ratio (IRR, 0.891, 95% CI, 0.594-1.335). Incident cases among both students and staff were highly correlated with community rates (Figure 2). In multivariable regression models controlling for community incidence, the risk of COVID-19 among students in districts with ≥3 versus ≥6 feet of distancing was similar (adjusted IRR, 0.904, 95% CI, 0.616-1.325) (Table 3). The model for staff controlling for community incidence also showed a similar risk with ≥3 versus ≥6 feet of distancing (adjusted IRR, 1.015, 95% CI, 0.754-1.365). After adjusting for the proportion of children aged 5-17 living in poverty and the racial and ethnic distribution of students within the districts, the effect estimate for the IRR changed by >10% but results remained non-significant (students: adjusted IRR, 0.789, 95% CI, 0.528-1.179). In the adjusted models, the IRR ratio for staff did not change (adjusted IRR, 0.915, CI, 0.669-1.252). Incidence rate ratios for the two distancing policies were similar in the sensitivity analyses, including the sensitivity analysis that included districts that adopted intermediate distancing policies (e.g., 4-5 feet) (Table 3).

Discussion:

In June, 2020 the Massachusetts DESE released guidance for re-opening schools that included universal masking of staff and for most students and recommended ≥3 to 6 feet of distancing between students. Due to the inherent flexibility in the DESE recommendations, application of physical distancing interventions varied throughout the state of Massachusetts. In this retrospective cohort study, we leveraged this variation to evaluate the effectiveness of different physical distancing recommendations on SARS-CoV-2 incidence rates in students and school staff participating in any in-person learning. Using case-report data from DESE and combining it with a manually-validated dataset with detailed district infection control plans, we found that adoption of greater physical distancing between individuals in school buildings was not associated with significantly reduced rates of SARS-CoV-2 among students and staff.

National and international guidance on distancing in schools is varied. The WHO recommends 1 meter (3.3 feet) of distancing in school settings while conversely, CDC

guidance recommends 6 feet of distance “to the greatest extent possible,” and the American Academy of Pediatrics recommends 3-6 feet [6–8]. Several countries have published data on case rates among school children with various physical distancing recommendations after school re-opening, although studies directly comparing different policies are limited. In Australia, New South Wales, children were recommended to distance 1.5 meters; a study evaluating SARS-CoV-2 transmission and secondary attack rates in children who attended schools and early childhood care settings while considered infectious found low rates of transmission, with a secondary attack rate of 1.2% [20,21]. In educational settings in England during the summer half term, children were advised to maintain distance “as able;” and universal masking was not required. Reported infections and outbreaks with a limited distancing policy were low, with 113 cases of infection and 55 outbreaks, among a large population (median daily student school attendance of 929,000) [22]. Similarly, in Singapore educational settings, where students adopted 3-6 feet of distancing, case rates were low, with identification of only three potential transmission incidents in three disconnected educational settings [23].

Our study adds to the literature as we were able to directly compare the impact of different physical distancing policies while controlling for other important mitigation measures, notably universal masking among staff and near universal masking among students, including close in younger grades. Our finding of no significant difference in student or staff case rates between schools with ≥3 versus ≥6 feet of distancing with a large sample size suggests that the lower physical distancing recommendation can be adopted in school settings without negatively impacting safety.

While incidence rates in both students and staff were lower than cases in surrounding communities, we found a strong correlation between community rates and positive cases in schools, particularly among school staff. Community transmission contributes to the number of individuals who enter the school building infected with SARS-CoV-2. A variety of factors may drive the relationship between community incidence and cases introduced into schools, including mandated compliance with mitigation measures,

such as masking and symptom screening. The finding of the strong correlation between community incidence and incidence in schools does not, however, imply that there is increased transmission in schools when community disease prevalence is high, nor that community metrics should dictate school opening/closing policies.

These findings have important implications for national policy for SARS-CoV-2 infection control recommendations applied to school settings. The practical implication of a 6 feet of distancing recommendation is that many schools are unable to open for full-in person learning, or at all, due to physical limitations of school infrastructure. This is particularly true in public school districts, which are unable to limit the number of students enrolled, compared to private schools, which have been able to more successfully open with 6 feet of distance between individuals [24]. Three-feet of physical distancing is more easily achieved in most school districts, including public ones, and thus, relaxing distancing requirements would likely have the impact of increasing the number of students who are able to benefit from additional in-person learning. Our data also suggest that intermediate distances (4 or 5 feet) can also be adopted without negatively impacting safety; adoption of intermediate distancing policies might be leveraged as a step-wise approach to return more students to the classroom.

Our study was limited by lack of complete data on potential cases among students and school staff; only cases reported to the state were able to be included in our analysis, thus it is possible that some cases may have been missed. However, it is unlikely that cases were differentially missed in districts with 3 versus 6 feet, mitigating the impact of this limitation on our main study finding. We also did not have detailed contact tracing data available, and so were not able to determine if cases in students were due to transmissions that happened within the school environment or independent introductions from cases acquired in the community. During the study period, active surveillance programs were rare, and thus we were not able to identify asymptomatic cases that may have resulted from in-school transmission, or to measure the effectiveness of this intervention as a tool for controlling SARS-CoV-2 spread in school settings.

Additionally, we were not able to measure the impact of physical distancing stratified by school type (elementary, middle, high) or age group. Thus, it is possible that the intervention may be more effective in one school type or age group, however, the vast majority of the districts included in the study (98%) adopted the same distancing policy, suggesting that findings are broadly applicable. We were not able to fully exclude a small benefit of greater physical distancing requirements among student cases, however, due to our large sample size, we can conclude that more restrictive physical distancing policies would not have substantial impact on preventing cases in students attending in-person schooling. It is possible that districts that officially allowed ≥3 feet of distancing between students ultimately succeeded in attaining more distance between students, and our methods were only able to capture official policy, not real-world implementation of the policy. We also were not able to examine how lower distancing policies may have impacted school closures; it is possible that districts with lower distancing requirements closed more frequently, or required more quarantines, due to how SARS-CoV-2 exposures are defined. Finally, we were not able to fully evaluate the impact of other types of infection control interventions, due to a lack of variation across the state. In particular, we were not able to examine the impact of universal masking due to nearly 100% adoption of this intervention, however, data from other sources and other settings clearly highlights the importance of masking as a mitigation measure and that mask compliance in school settings is high [4,25].

Conclusions:

Increasing physical distancing requirements from 3 to 6 feet in school settings is not associated with a reduction in SARS-CoV-2 cases among students or staff, provided other mitigation measures, such as universal masking, are implemented. These findings may be used to update guidelines about SARS-CoV-2 mitigation measures in school settings.

NOTES

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Table 1. COVID-19 Daily Incidence Among Students and School Staff Participating in In-Person Instruction in Massachusetts as Reported to the Department of Elementary and Secondary Education

Week End Date	Daily Student Cases per 100,000; ≥6 feet of physical distancing	Daily Student Cases per 100,000; ≥3 feet of physical distancing	Daily Staff Cases per 100,000; ≥6 feet of physical distancing	Daily Staff Cases per 100,000; ≥3 feet of physical distancing
Sep 30, 2020	1.38	2.17	2.09	3.23
Oct 7, 2020	2.90	3.26	6.26	2.42
Oct 14, 2020	2.61	2.95	6.89	4.03
Oct 21, 2020	3.59	4.32	5.19	6.47
Oct 28, 2020	5.86	6.21	9.29	7.91
Nov 4, 2020	4.81	4.67	12.85	13.47
Nov 11, 2020	4.54	7.96	17.13	8.98
Nov 18, 2020	10.36	15.70	25.33	39.86
Nov 25, 2020	7.64	7.40	24.66	22.36
Dec 2, 2020	7.61	11.96	31.52	24.62
Dec 9, 2020	16.45	10.82	53.94	44.31
Dec 16, 2020	17.71	17.18	47.89	53.78
Dec 23, 2020	14.92	16.19	46.32	53.36
Jan 13, 2021	15.65	16.48	48.10	44.59
Jan 20, 2021	17.49	11.46	45.90	42.65
Jan 27, 2021	18.01	17.63	38.14	43.64

Table 2. Distribution of Infection Control Interventions Implemented in Massachusetts Public Schools with Any In-Person Instruction

Infection Control Intervention	**Districts**	**Students** (All districts)	**Students** ≥6 Feet	**Students** ≥3 Feet	**Staff** (All districts)	**Staff** ≥6 Feet	**Staff** ≥3 Feet
School Model[a]							
High on-campus enrollment	90	188,134	121,949	55,989	27,270	18,699	7,997
Lower on-campus enrollment	161	349,202	270,691	67,167	72,120	58,341	11,866
Elementary, Middle, and High School All in the Same Model	188	450,881	327,416	105,331	82,907	64,118	16,823
Universal Masking[b]							
Among all staff	251	537,336	392,640	123,156	99,390	77,040	19,863
Among all students	251	537,336	392,640	123,156	99,390	77,040	19,863
Physical Distancing							
≥6 Feet	194	392,640	392,640	--	77,040	77,040	--
≥3 Feet	48	123,156	--	123,156	19,863	--	19,863
Other (4-5 feet)	9	21,540	--	--	2,487	--	--
Enhanced Cleaning Protocol[c]	218	445,916	343,834	80,542	78,290	62,521	13,282
Cohorting (Any)	214	483,042	357,384	104,500	88,264	69,486	16,605
Mandatory Symptom Screens Prior to Entering School Buildings	223	492,223	368,688	105,161	91,428	72,832	16,533
Ventilation Interventions[d]	205	430,264	334,404	79,309	76,539	60,891	13,189
Surveillance Testing	5	7,310	6,582	728	2,307	2,181	126
Universal Vaccination Policy[e]	251	537,336	392,640	123,156	99,390	77,040	19,863
District Demographic Variables[f]							
Children ages 5-17 in poverty (%)		10.47	10.24	12.13	--	--	--

White (%)		65.25	65.10	64.09	--	--	--
Black (%)		6.97	7.36	5.76	--	--	--
Asian (%)		7.58	7.91	6.34	--	--	--
Other (%)		4.23	4.32	3.909	--	--	--
Hispanic (%)		15.99	15.33	19.93	--	--	--

[a] High on-campus enrollment is defined as districts with an average of at least 80% of their total enrolled students participating in on-campus instruction throughout the time period. Lower on-campus enrollment is defined as districts with an average of less than 80% of enrolled students participating in on-campus instruction.

[b] During the study period, universal masking among staff and students grades two and higher was a pre-requisite for approval to open schools according to Department of Elementary and Secondary Education. Many districts opted to require (69.7%) or strongly recommend (26.3%) masking among students in younger grade levels.

[c] Cleaning protocols were variably defined but recorded if the district reported any enhanced protocols beyond usual practices.

[d] Ventilation interventions were highly heterogeneous and included requirements to open windows, purchase HEPA filters, plans for HVAC upgrades, and plans to move classrooms to outdoor spaces.

[e] Universal influenza vaccination for all students was mandated in the state of Massachusetts during the Fall of 2020. The requirement was later waived due to low rates of influenza during the 2020-2021 influenza season.

[f] Demographics variables obtained from NCES at the district level

Table 3. Regression Analysis

	IRR[a], Students (unadjusted for community incidence)	IRR, Students (adjusted for community incidence)[b]	IRR Staff (unadjusted for community incidence)	IRR Staff (adjusted for community incidence)
≥6 Feet of Physical Distancing, all Districts (N=3,625)[c,d]	0.891 (0.594 – 1.335)	0.904 (0.616 - 1.325)	0.989 (0.733 – 1.334)	1.015 (0.754-1.365)
≥6 Feet of Physical Distancing, adjusted for district demographics (N=3,612)[e]	0.761 (0.500-1.157)	0.789 (0.528-1.179)	0.902 (0.663-1.226)	0.915 (0.669-1.252)
≥6 Feet of Physical Distancing, excluding districts with surveillance testing (N=3,554)[d]	0.879 (0.587 – 1.315)	0.891 (0.609 - 1.304)	0.971 (0.721 – 1.307)	0.997 (0.743-1.338)
≥6 Feet of Physical Distancing versus < 6 feet of distancing (N=3,763)[f]	0.983 (0.665 – 1.453)	0.976 (0.678 - 1.407)	1.096 (0.818 – 1.467)	1.103 (0.830-1.466)

All regressions adjusted for week. Standard errors adjusted for clustering by school district.

[a] IRR= Incidence rate ratio

[b] adjusted for community incidence by week

[c] N=Number of district-weeks included in the regression

[d] 3 feet of physical distancing referent group

[e] Demographic variables included in the model, of total enrolled students: % Black, % Hispanic, % Asian, % Other (Native American, Native Alaskan, Native Hawaiian, Pacific Islander, Two or more races, Unknown, and Other), and % of children 5-17 in poverty. One district is missing poverty data and was dropped from the regression

[f] <6 feet of physical distancing referent group

Figure 1 Legend. Incidence of COVID-19 Cases Among Students and School Staff, by Physical Distancing, Reported to DESE During the First 16 Weeks of the 2020-21 Academic Year

Figure 2 Legend. Incidence of COVID-19 cases Among Students and School Staff Reported to DESE During the First 16 Weeks of the 2020-21 Academic Year

Figure 1

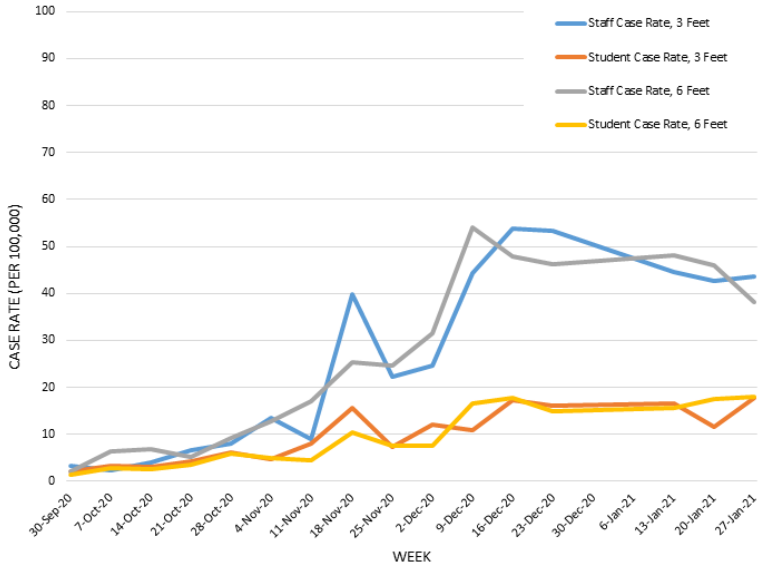
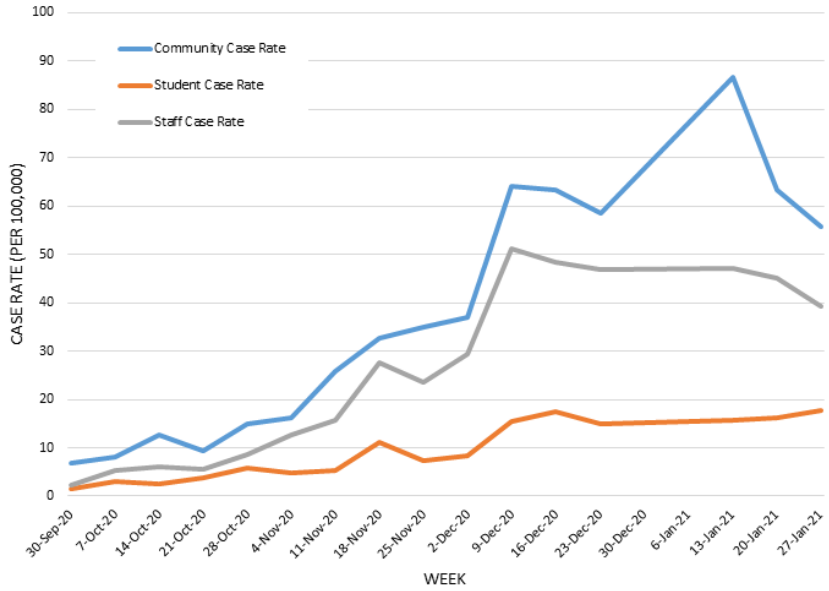


Figure 2



JAMA | Original Investigation

Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

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IMPORTANCE Convalescent plasma is a proposed treatment for COVID-19.

OBJECTIVE To assess clinical outcomes with convalescent plasma treatment vs placebo or standard of care in peer-reviewed and preprint publications or press releases of randomized clinical trials (RCTs).

DATA SOURCES PubMed, the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform were searched until January 29, 2021.

STUDY SELECTION The RCTs selected compared any type of convalescent plasma vs placebo or standard of care for patients with confirmed or suspected COVID-19 in any treatment setting.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data on relevant clinical outcomes, trial characteristics, and patient characteristics and used the Cochrane Risk of Bias Assessment Tool. The primary analysis included peer-reviewed publications of RCTs only, whereas the secondary analysis included all publicly available RCT data (peer-reviewed publications, preprints, and press releases). Inverse variance–weighted meta-analyses were conducted to summarize the treatment effects. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation.

MAIN OUTCOMES AND MEASURES All-cause mortality, length of hospital stay, clinical improvement, clinical deterioration, mechanical ventilation use, and serious adverse events.

RESULTS A total of 1060 patients from 4 peer-reviewed RCTs and 10 722 patients from 6 other publicly available RCTs were included. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the 4 peer-reviewed RCTs was 0.93 (95% CI, 0.63 to 1.38), the absolute risk difference was −1.21% (95% CI, −5.29% to 2.88%), and there was low certainty of the evidence due to imprecision. Across all 10 RCTs, the summary RR was 1.02 (95% CI, 0.92 to 1.12) and there was moderate certainty of the evidence due to inclusion of unpublished data. Among the peer-reviewed RCTs, the summary hazard ratio was 1.17 (95% CI, 0.07 to 20.34) for length of hospital stay, the summary RR was 0.76 (95% CI, 0.20 to 2.87) for mechanical ventilation use (the absolute risk difference for mechanical ventilation use was −2.56% [95% CI, −13.16% to 8.05%]), and there was low certainty of the evidence due to imprecision for both outcomes. Limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences.

CONCLUSIONS AND RELEVANCE Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

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Supplemental content

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Patients with COVID-19 have frequently been treated with convalescent plasma (ie, plasma from persons who have recovered from SARS-CoV-2 infection), but the clinical evidence of benefits or harms is limited.[1] Preliminary reports indicating that convalescent plasma is well tolerated with low risk of adverse events[2] led to Emergency Use Authorization in the US in August 2020.[3] Despite the large number of clinical trials being conducted since the start of the pandemic, only a few have been published in peer-reviewed journals and some have posted preliminary results on preprint servers.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) platform trial is by far the largest clinical trial on COVID-19 treatments, and has provided important evidence for several promising treatments, including dexamethasone,[4] hydroxychloroquine,[5] lopinavir-ritonavir,[6] and azithromycin.[7] The part of the trial investigating treatment with convalescent plasma was halted based on the recommendation of the RECOVERY data monitoring committee. Communicated as a press release on January 15, 2021, the preliminary reported results based on data from 10 406 patients indicate no significant association of a benefit with convalescent plasma in reducing all-cause mortality compared with standard of care (risk ratio [RR], 1.04; 95% CI, 0.95-1.14).[8]

Given the previously reported clinical trials and this recent announcement,[8] a systematic review and meta-analysis was conducted to summarize and assess all published evidence from randomized clinical trials (RCTs) on the association between treatment with convalescent plasma compared with standard of care or placebo on clinical outcomes in patients with COVID-19.

Key Points

Question Is treatment with convalescent plasma associated with improved clinical outcomes?

Findings In a meta-analysis of 4 peer-reviewed and published randomized clinical trials including 1060 patients with COVID-19 treated with convalescent plasma vs control, the risk ratio for mortality was 0.93 and after the addition of 6 unpublished randomized clinical trials and 10 722 patients, the risk ratio for mortality was 1.02; neither finding was statistically significant. No significant associations with benefit were shown for hospital length of stay, mechanical ventilation use, clinical improvement, or clinical deterioration.

Meaning Among patients with COVID-19, treatment with convalescent plasma compared with control was not associated with improved survival or other positive clinical outcomes.

Methods

This review has been reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis.[9]

Search Strategy and RCT Selection

Two reviewers (P.J. and C.A.) systematically searched PubMed (using peer-review of electronic search strategies[10]), the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform for all published RCTs as of January 29, 2021, aiming to assess the benefits and harms of convalescent plasma to treat patients with COVID-19. Search strategies were designed with terms related to convalescent plasma and COVID-19 along with standard RCT filters (eMethods in the Supplement).

In addition, we searched for press releases presenting results of RCTs assessing convalescent plasma. Peer-reviewed publications, preprints, and press releases were eligible for inclusion. There were no restrictions on language or geographic region.

The selected RCTs included patients with suspected or confirmed SARS-CoV-2 infection randomly allocated to receive convalescent plasma, placebo together with standard of care, or only standard of care. The RCTs were included regardless of the level of plasma titer (ie, low or high antibody titer) or health care setting. The RCTs aimed at preventing the occurrence of COVID-19 were excluded.

Outcomes

The outcomes were all-cause mortality at any time point, length of hospital stay, number of patients with clinical improvement or deterioration, number of patients requiring mechanical ventilation, and number of patients experiencing serious adverse events.

Data Extraction and Risk of Bias Assessment

We extracted the following information for each RCT: trial design characteristics (randomization procedure and blinding), descriptions of the experimental and control groups, baseline characteristics of the patients, eligibility criteria for plasma donors, and trial location. High antibody titer was defined in this meta-analysis as S-protein receptor-binding domain-specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher. For each outcome, we collected either the number of events for the convalescent plasma and control groups or the effect size and corresponding 95% CI (only hazard ratios [HRs] were consistently reported for length of hospital stay). Data on outcomes (F.E. and M.H.) and characteristics (A.M.S. and V.G.) were extracted independently by 2 reviewers.

For each RCT, 2 reviewers (A.M.S. and V.G.) independently assessed the risk of bias for all-cause mortality, mechanical ventilation use, and length of hospital stay using version 2 of the Cochrane Risk of Bias Assessment Tool (low risk, some concerns, or high risk of bias).[11] We also used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[12] to assess the certainty of the evidence for the summarized outcomes regarding the treatment effect of convalescent plasma on patients with COVID-19.

Disagreements among reviewers were discussed with a third reviewer (P.J.) until a consensus was reached.

Statistical Analyses

The primary analysis included only RCTs published in peer-reviewed journals. A secondary analysis included all the RCTs (peer-reviewed, preprints, and information from the press release for the RECOVERY trial).

For outcomes with available data (all-cause mortality, length of hospital stay, and mechanical ventilation use), we conducted meta-analyses to summarize the treatment effects using RRs and HRs when applicable. The treatment effects for clinical improvement, clinical deterioration, and serious adverse events were not summarized due to inconsistent definitions of these outcomes and insufficient reporting of relevant details. When possible (based on the available data), we also estimated and summarized the treatment effects across the RCTs on an absolute risk difference scale.

We conducted inverse variance-weighted random-effects meta-analyses using the Paule and Mandel τ^2 estimator for heterogeneity.[13] We applied the Hartung-Knapp adjustment[14] to account for uncertainties due to large variations in sample size and in the number of outcome events across the RCTs. Heterogeneity across the RCTs was described using the I^2 and τ^2 metrics.[15]

We conducted sensitivity analyses to assess the robustness of the results using the following meta-analytic models: Sidik-Jonkman τ^2 estimator (instead of the Paule and Mandel estimator), the profile likelihood model, and the inverse variance-weighted fixed-effects model.

All tests were 2-sided and statistical significance was based on the 95% CIs excluding the null. All analyses were conducted using R version 3.6.2 meta and metafor packages (R Foundation for Statistical Computing).

Results

A total of 4357 records were identified in databases, registries, and other sources. There were 4 RCTs published in peer-reviewed journals[16-19] and 5 RCTs published as preprints[20-24] that were included. In addition, press releases were identified for 2 RCTs (the RECOVERY trial[8] and the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP][25]) but only the reported results from the RECOVERY trial[8] (NCT04381936) were included, stating 1873 deaths among 10 406 patients randomized (eFigure 1 in the Supplement).

Of the 10 included RCTs, 3 were conducted in India, 2 in Argentina, and 1 each in Bahrain, China, the Netherlands, Spain, and the UK (**Table 1**). Five RCTs were terminated early; 2 were terminated early due to futility (Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease [ConCOVID; NCT04342182][22] and RECOVERY [NCT04381936][8]) and 3 were terminated early due to slow recruitment (Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients [ConPlas-19; NCT04345523],[23] ChiCTR2000029757,[19] and NCT04479163).[16] There were 2 double-blind RCTs (NCT04479163 and Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia [PlasmAr; NCT04383535]),[18] whereas the other 8 were open-label RCTs.

From the 4 RCTs published in peer-reviewed journals, there were 1060 patients (595 randomized to convalescent plasma and 465 to placebo together with standard of care or only standard of care). From the 5 RCTs published as preprints, there were 316 patients (155 randomized to convalescent plasma and 161 to placebo together with standard of care or only standard of care). From the RECOVERY trial, there were 10 406 patients (the number of patients randomized per group was not reported in the press release information).

Of the 10 RCTs, 9 included only patients with confirmed SARS-CoV-2 infection but the RECOVERY trial included those with either confirmed or suspected SARS-CoV-2 infection. Only 1 RCT included outpatients, 5 included inpatients requiring supplemental oxygen, and 4 included inpatients regardless of need for supplemental oxygen (Table 1). Patients were administered a single convalescent plasma transfusion in 5 of the RCTs and were administered 2 transfusions 24 hours apart in the other 5 RCTs (Table 1). Of the 10 RCTs, high plasma titer was used in 4, low titer was used in 1, a minimum plasma titer cutoff was not used in 3, and it was unclear in 2 (Table 1). Six RCTs used donated plasma from men, nulliparous women, or women testing negative for HLA antibodies (this type of description was not reported for 4 RCTs: RECOVERY [NCT04381936], NCT04479163, ChiCTR2000029757, and ConPlas-19 [NCT04345523]). Only 3 RCTs (PlasmAr [NCT04383535], NCT04356534, and PLACID [CTRI/2020/04/024775]) reported the COVID-19 severity of plasma donors.

Detailed information on patient characteristics were available for 9 of the 10 RCTs (**Table 2**). The mean age of patients was younger than 70 years and they were typically male (≤80%); these generalizations did not apply to NCT04479163. Comorbidities at randomization were common when reported in the trials and only 2 RCTs reported the concurrent treatments at randomization.

Risk of Bias

The risk of bias for mortality, length of hospital stay, and mechanical ventilation use was deemed low for 7 of the 10 RCTs. For 2 of the RCTs, the risk of bias was classified as having some concerns (NCT04356534 and ConPlas-19 [NCT04345523]) and for 1 RCT it was deemed high (Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease [PICP19; CTRI/2020/05/025209]; **Figure 1**). Loss to follow-up was less than 10% when reported in 9 RCTs (data were unavailable for the RECOVERY trial).

The RECOVERY trial was deemed as having probably low risk of bias based on the trial protocol and published information for other treatments assessed by the trial (Figure 1).[4-6,26,27]

Data Availability

Mortality was assessed in all 10 RCTs and for 8 of the trials it was assessed between 15 to 30 days after randomization (1 RCT assessed mortality at 60 days and 1 RCT did not report length of follow-up; eTable 1 in the Supplement). Length of hospital stay was assessed in 7 RCTs; 3 used medians or means (1 published in a peer-reviewed journal and 2 published as preprints), 1 used HRs (published as a preprint), and 3 used both medians and HRs (2 published in peer-reviewed journals and 1 published as a preprint). The need for mechanical ventilation use was reported in 5 RCTs (3 peer-reviewed and 2 preprints). Data on clinical deterioration and

Table 1. Characteristics of the 10 Trials

	Trial registration No. (study acronym)[a]									
	ChiCTR 2000029757[19]	NCT 04479163[16]	NCT 04383535 (PlasmAr)[18]	CTRI /2020/04/ 024775 (PLACID)[17]	NCT 04345523 (ConPlas-19)[23]	NCT 04346446 (ILBS-COVID-02)[21]	NCT 04356534[20]	NCT 04342182 (ConCOVID)[22]	CTRI /2020/05/ 025209 (PICP19)[24]	NCT 04381936 (RECOVERY)[8]
Publication format	Journal	Journal	Journal	Journal	Preprint	Preprint	Preprint	Preprint	Preprint	Press release
Peer-reviewed	Yes	Yes	Yes	Yes	No	No	No	No	No	No
No. included	103	160	333	464	81	29	40	86	80	10 406
No. planned for inclusion	200	210	333	452	278	40	40	426	80	20 000
Setting	Hospitalized	Outpatient	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized
Oxygen supplementation	All patients	None	Some patients	All patients	Some patients	All patients	All patients	Some patients	All patients	Some patients
Plasma titer[b]	High	High: >1:1000	High: ≥1:800 (RBD)	No minimum	High: ≥1:80 neutralizing	No minimum	No minimum	Low: ≥1:400 RBD	Unclear	Unclear
Dose description	Single transfusion of 4-13 mL/kg	Single transfusion of 250 mL	Single transfusion of 5-10 mL/kg (minimum, 400 mL; maximum, 700 mL)	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 250-300 mL	Two transfusions of 500 mL administered 24 h apart	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 300 mL[c]	Two transfusions of 200 mL administered 24 h apart	Two transfusions of 275 mL (±75 mL) administered 24 h apart
Treatment since symptom onset	Any time	≤72 h	Any time	Any time	≤12 d	≤3 d	≤14 d	Any time	≤14 d	Any time
Type of control	Standard of care	Placebo and standard of care	Placebo and standard of care	Standard of care	Standard of care	Placebo and standard of care	Standard of care	Standard of care	Standard of care	Standard of care

Abbreviations: ConCOVID, Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RBD, receptor-binding domain; RECOVERY, Randomized Evaluation of COVID-19 Therapy.

[a] Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications.

[b] High was defined in this meta-analysis as S-protein RBD–specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher.

[c] The COVIDAR IgG test was used to determine the dose.

Table 2. Patient Baseline Characteristics in 9 Trials

	Trial registration No. (study acronym)[a]								
	ChiCTR 2000029757[19]	NCT04479163[16]	NCT04383535 (PlasmAr)[18]	CTRI/2020/04/024775 (PLACID)[17]	NCT04345523 (ConPlas-19)[23]	NCT04346446 (ILBS-COVID-02)[21]	NCT04356534[20]	NCT04342182 (ConCOVID)[22]	CTRI/2020/05/025209 (PICP19)[24]
No. of patients randomized									
Convalescent plasma group	52	80	228	235	38	14	20	43	40
Control group[b]	51	80	105	229	43	15	20	43	40
Age, median (IQR), y									
Convalescent plasma group	70 (62-80)	76.4 (8.7)[c]	62.5 (53-72.5)	52 (42-60)	60.5 (46-74)	48.1 (9.1)[c]	52.6 (14.9)[c]	61 (56-70)	NR
Control group[b]	69 (63-76)	77.9 (8.4)[c]	62 (49-71)	52 (41-60)	58 (51-73)	48.3 (10.8)[c]	50.7 (12.5)[c]	63 (55-77)	NR
Sex, No. (%)									
Convalescent plasma group									
Male	27 (52)	26 (32)	161 (71)	177 (75)	20 (53)	11 (79)	17 (85)	29 (67)	30 (75)
Female	25 (48)	54 (68)	67 (29)	58 (25)	18 (47)	3 (21)	3 (15)	14 (33)	10 (25)
Control group[b]									
Male	33 (65)	34 (42)	64 (61)	177 (77)	24 (56)	11 (73)	15 (75)	33 (77)	27 (67)
Female	18 (35)	46 (58)	41 (39)	52 (23)	19 (54)	4 (27)	5 (25)	10 (23)	13 (33)
Type of mechanical ventilation use at randomization, No. (%)[d]									
Invasive									
Convalescent plasma group	14 (28)	0	0	0	0	0	0	5 (12)	0
Control group[b]	11 (22)	0	0	0	0	0	0	8 (19)	0
Noninvasive									
Convalescent plasma group	21 (41)	0	0	0	0	0	0	NR	0
Control group[b]	23 (46)	0	0	0	0	0	0	NR	0
Comorbidities at randomization, No. (%)									
Hypertension									
Convalescent plasma group	29 (56)	62 (78)	111 (49)	92 (39)	20 (53)	0	5 (25)	11 (26)	NR
Control group[b]	27 (53)	52 (65)	48 (46)	81 (35)	12 (28)	0	5 (25)	11 (26)	NR
Diabetes									
Convalescent plasma group	9 (17)	23 (29)	40 (18)	113 (48)	12 (32)	0	7 (35)	13 (30)	NR
Control group[b]	12 (24)	13 (16)[e]	21 (20)	87 (38)	5 (12)	0	9 (45)	8 (19)	NR
Cardiac disease									
Convalescent plasma group	14 (27)	14 (18)[e]	8 (4)	15 (6)	6 (16)	0	2 (10)	9 (21)	NR
Control group[b]	12 (24)	7 (9)[e]	3 (3)	17 (7)	9 (21)	0	2 (10)	11 (26)	NR

(continued)

Table 2. Patient Baseline Characteristics in 9 Trials (continued)

	Trial registration No. (study acronym)[a]								
	ChiCTR 2000029757[19]	NCT04479163[16]	NCT04383535 (PlasmAr)[18]	CTRI/2020/04/024775 (PLACID)[17]	NCT04345523 (ConPlas-19)[23]	NCT04346446 (ILBS-COVID-02)[21]	NCT04356534[20]	NCT04342182 (ConCOVID)[22]	CTRI/2020/05/025209 (PICP19)[24]
Pulmonary disease[f]									
Convalescent plasma group	NR	5 (6)	32 (14)	8 (3)	2 (5)	0	3 (15)	12 (28)	NR
Control group[b]	NR	8 (10)	7 (7)	7 (3)	8 (19)	0	0	11 (26)	NR
Chronic kidney failure									
Convalescent plasma group	2 (4)	1 (1)	10 (4)	8 (3)	2 (5)	0	1 (5)	1 (2)	NR
Control group[b]	4 (8)	3 (4)[e]	4 (4)	9 (4)	2 (5)	0	1 (5)	6 (14)	NR
Cancer									
Convalescent plasma group	3 (6)	4 (5)	27 (12)	1 (<1)	NR	0	NR	5 (12)	NR
Control group[b]	0	2 (2)	14 (14)	0	NR	0	NR	3 (7)	NR
Liver disease									
Convalescent plasma group	5 (10)	0	NR	0	NR	NR	0	1 (2)	NR
Control group[b]	5 (10)	0	NR	0	NR	NR	0	0	NR
Risk factors at randomization, No. (%)									
Smoker[g]									
Convalescent plasma group	NR	13 (16)	107 (47)	19 (8)	NR	NR	0	NR	NR
Control group[b]	NR	10 (12)	43 (41)	18 (8)	NR	NR	0	NR	NR
Body mass index >30[h]									
Convalescent plasma group	NR	4 (5)	104 (46)	16 (7)	NR	NR	NR	NR	NR
Control group[b]	NR	8 (10)[e]	52 (50)	17 (7)	NR	NR	NR	NR	NR

Abbreviations: ConCOVID, Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; NR, not reported; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia.

[a] Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. Only 3 trials reported concurrent treatments at randomization. Of 81 patients in ConPlas-19, 70 (86.4%) received hydroxychloroquine, 50 (61.7%) received azithromycin, and 46 received (56.8%) corticosteroids. Of 103 patients in ChiCTR2000029757, 85 (82.5%) received antiviral drugs, 77 (74.8%) received antibacterial or antibiotic drugs, and 37 (35.9%) received corticosteroids. Of 333 patients in PlasmAr, 9 (2.7%) received corticosteroids. Information on patient baseline characteristics were not available for the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial because the results were communicated as a press release.

[b] Placebo together with standard of care or only standard of care.

[c] Reported as mean (SD).

[d] Categorized according to what was reported in the trial reports.

[e] The denominator was 79 patients.

[f] Includes chronic obstructive pulmonary disease, asthma, and tuberculosis.

[g] Includes current and former smokers.

[h] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Risk of Bias Assessments for the Outcomes of All-Cause Mortality, Length of Hospital Stay, and Mechanical Ventilation Use

	Trial registration No. or study acronym									
Risk of bias domain (assessments for the effect of assignment to intervention)	ChiCTR2000029757[19]	NCT04479163[16]	PlasmAr[18]	PLACID[17]	ConPlas-19[23]	ILBS-COVID-02[21]	NCT04356534[20]	ConCOVID[22]	PICP19[24]	RECOVERY[8]
1. Randomization process	Low	Low	Low	Low	Some concerns	Low	Some concerns	Low	Some concerns	Low
2. Deviations from the intended interventions	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	NA
3. Missing outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	NA
4. Measurement of the outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
5. Selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Overall risk of bias	Low	Low	Low	Low	Some concerns[a]	Low	Some concerns[a]	Low	High risk[b]	Probably low risk[c]

Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. ConCOVID indicates Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; NA, not available; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RECOVERY, Randomized Evaluation of COVID-19 Therapy.

[a] There was no detailed information reported regarding (1) the randomization process or (2) the concealment of randomized assignment.

[b] There was no detailed information reported regarding (1) the randomization process, (2) the concealment of randomized assignment, (3) the flow of patients through the trial, and (4) possible deviations from the intended interventions due to the open-label setting of the trial.

[c] The results were communicated as a press release. The assessment of this trial considered the study protocol and publications reporting results from other treatment groups of the trial.[4-6,26,27]

clinical improvement were available in 5 RCTs (3 peer-reviewed and 2 preprints) and 3 RCTs reported data on serious adverse events (1 peer-reviewed and 2 preprints).

Association of Convalescent Plasma With Clinical Outcomes

In the primary analysis including only peer-reviewed RCTs, the mortality in patients receiving convalescent plasma was 11.6% (69/595) and 12.7% (59/465) in control patients. The summary RR for all-cause mortality with convalescent plasma was 0.93 (95% CI, 0.63 to 1.38; P = .60) and the absolute risk difference was −1.21% (95% CI, −5.29% to 2.88%). There was no significant between-trial heterogeneity (I^2 = 0%; τ^2 = 0 [95% CI, 0 to 1.35]) (**Figure 2**A). In the RECOVERY trial, the reported 28-day mortality rates were 18% with convalescent plasma and 18% for usual care (control).

Across the 10 RCTs, the summary RR for all-cause mortality with convalescent plasma was 1.02 (95% CI, 0.92 to 1.12]; P = .68). There was no significant between-trial heterogeneity (I^2 = 0%; τ^2 = 0 [95% CI, 0 to 0.86]). In this meta-analysis of the 10 RCTs for all-cause mortality, the RECOVERY trial accounted for 90.2% of the weight and 88.3% (10 406/11 782) of the patients (Figure 2). The results of the sensitivity analyses were consistent with the main results (eTable 2 in the Supplement).

The 4 peer-reviewed RCTs showed no significant associations between treatment with convalescent plasma and reductions in length of hospital stay (summary HR, 1.17 [95% CI, 0.07 to 20.34], P = .61 for analysis of 436 patients) or mechanical ventilation use (summary RR, 0.76 [95% CI, 0.20 to 2.87], P = .35 for analysis of 957 patients) (Figure 2). The absolute risk difference for mechanical ventilation use was −2.56% (95% CI, −13.16% to 8.05%). Similar results were observed for the peer-reviewed and preprint RCTs for length of hospital stay (HR, 1.07 [95% CI, 0.79 to 1.45], P = .87 for analysis of 603 patients) and for mechanical ventilation use (RR, 0.81 [95% CI, 0.42 to 1.58], P = .88 for analysis of 1026 patients; Figure 2). The absolute risk difference for mechanical ventilation use was −2.21% (95% CI, −8.94% to 4.51%) (eFigure 2 in the Supplement).

For clinical improvement and clinical deterioration, the RRs were not summarized across RCTs due to inconsistent definitions and insufficient reporting of relevant details for these outcomes (eTable 1 and eFigure 3 in the Supplement). Of the 5 RCTs (3 peer-reviewed and 2 preprints) that reported such data, none demonstrated statistically significant clinical deterioration or improvement in patients who received convalescent plasma compared with the control group and the 95% CIs were wide (eFigure 3 in the Supplement).

No meta-analysis was conducted on serious adverse events due to inconsistencies in the reporting. PlasmAr (NCT04383535), ConPlas-19 (NCT04345523), and ConCOVID (NCT04342182) were the RCTs that reported data on serious adverse events (eFigure 4 in the Supplement); 60 serious adverse events were reported for the 309 patients in the convalescent plasma groups and 26 serious adverse events were reported for the 191 patients in the control groups. Even though ConCOVID (NCT04342182) included all-cause mortality in its definition of serious adverse events and 17 patients died, only plasma-related serious adverse events were reported (with 0 events). Similarly, PLACID (CTRI/2020/04/024775) and NCT04356534 reported recording serious adverse events including all-cause mortality but no clear data were shown.

The Certainty of the Evidence

For the primary analysis that only included the 4 RCTs published in peer-reviewed journals, the certainty of the evidence (using GRADE) for mortality was low due to very serious imprecision concerns regarding the wide 95% CI for the summary RR, which would be compatible with substantial benefit or harm. For the secondary analysis that included all 10 RCTs (published in peer-reviewed journals, published as preprints, and the RECOVERY trial), the concern regarding imprecision was reduced and the certainty of the evidence was rated as moderate (eTable 3 in the Supplement).

For length of hospital stay and mechanical ventilation use, the certainty of the evidence was rated as low for peer-reviewed trials only and when considering all publicly available trials due to very serious imprecision concerns (wide 95% CIs for the summary RR estimates; eTable 3 in the Supplement).

Discussion

In this meta-analysis that included 4 RCTs published in peer-reviewed journals for the primary analysis and an additional 6 RCTs not published in peer-reviewed journals (5 preprints and 1 press release) for the secondary analysis, treatment with convalescent plasma compared with placebo in combination with standard of care or only standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes among patients with COVID-19.

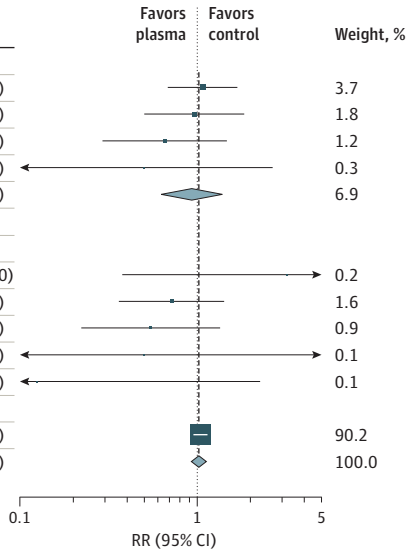
The certainty of the evidence on all-cause mortality was low when only the peer-reviewed trials were included and then moderate when the evidence from the RCTs published as preprints and the RECOVERY trial was added. The evidence was largely dominated by the RECOVERY trial, which accounted for 90.2% of the weight in the meta-analysis, although the pooled results from the 4 peer-reviewed trials were similar. The results from the RECOVERY trial published as a press release warrant cautious interpretation until the trial results are fully analyzed and reported in a peer-reviewed journal.

There also was no significant association of convalescent plasma with benefits on other patient-relevant clinical outcomes, including reduction in the length of hospital stay or mechanical ventilation use; however, summarized sample sizes were considerably smaller (range, 603-1026 patients) than for all-cause mortality (11 782 patients). Data on clinical improvement or deterioration were limited and inconclusive due to the use of inconsistent definitions for the outcomes and insufficient reporting of the relevant details for these outcomes. Similarly, the safety of convalescent plasma regarding serious adverse events could not be reliably assessed because only 3 RCTs reported data and there were inconsistencies in the definitions used. Although it was identified during the literature search, the press release for the REMAP-CAP trial[25] was not

Figure 2. Association of Convalescent Plasma With All-Cause Mortality, Length of Hospital Stay, and Mechanical Ventilation Use in Peer-Reviewed Trials and Non–Peer-Reviewed Trials (Preprints and the RECOVERY Trial)

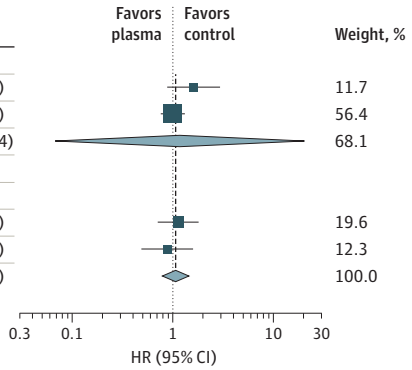
A All-cause mortality

Trial	Events, No./total: Plasma	Control	RR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
PLACID[17]	34/235	31/229	1.07 (0.68-1.68)	3.7
PlasmAr[18]	25/228	12/105	0.96 (0.50-1.83)	1.8
ChiCTR2000029757[19]	8/52	12/51	0.65 (0.29-1.47)	1.2
NCT04479163[16]	2/80	4/80	0.50 (0.09-2.65)	0.3
Summary for peer-reviewed studies			0.93 (0.63-1.38)	6.9
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .65$				
Studies published as preprints				
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)	0.2
PICP19[24]	10/40	14/40	0.71 (0.36-1.41)	1.6
ConCOVID[22]	6/43	11/43	0.55 (0.22-1.34)	0.9
NCT04356534[20]	1/20	2/20	0.50 (0.05-5.08)	0.1
ConPlas-19[23]	0/38	4/43	0.13 (0.01-2.26)	0.1
Study published as press release				
RECOVERY[8]	NA/NA	NA/NA	1.04 (0.95-1.14)	90.2
Summary for all studies			1.02 (0.92-1.12)	100.0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$				
Test for overall effect: $P = .68$				



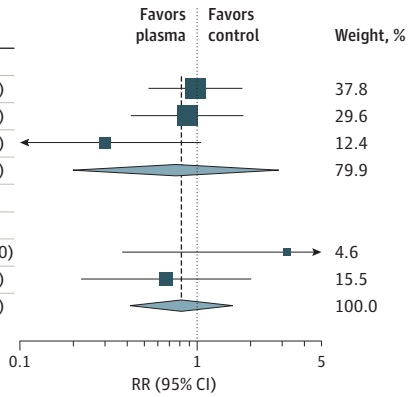
B Length of hospital stay

Trial	Events, No./total: Plasma	Control	HR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
ChiCTR2000029757[19]	NA/52	NA/51	1.61 (0.88-2.95)	11.7
PlasmAr[18]	NA/228	NA/105	1.00 (0.76-1.32)	56.4
Summary for peer-reviewed studies			1.17 (0.07-20.34)	68.1
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 0.0559$, $P = .16$				
Studies published as preprints				
ConPlas-19[23]	NA/38	NA/43	1.13 (0.71-1.80)	19.6
ConCOVID[22]	NA/43	NA/43	0.88 (0.49-1.59)	12.3
Summary for all studies[a]			1.07 (0.79-1.45)	100.0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$				
Test for overall effect: $P = .55$				



C Mechanical ventilation use

Trial	Events, No./total: Plasma	Control	RR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
PLACID[17]	19/235	19/229	0.97 (0.53-1.79)	37.8
PlasmAr[18]	19/228	10/105	0.87 (0.42-1.82)	29.6
NCT04479163[16]	3/80	10/80	0.30 (0.09-1.05)	12.4
Summary for peer-reviewed studies			0.76 (0.20-2.87)	79.9
Heterogeneity: $I^2 = 29\%$, $\tau^2 = 0.1194$, $P = .25$				
Studies published as preprints				
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)	4.6
NCT04356534[20]	4/20	6/20	0.67 (0.22-2.01)	15.5
Summary for all studies[a]			0.81 (0.42-1.58)	100.0
Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0559$, $P = .34$				
Test for overall effect: $P = .44$				



Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. Hartung-Knapp adjustment was used for the random-effects model and the Paule-Mandel estimator was used for τ^2. The weight percentages correspond to the secondary analysis for all studies. ConCOVID indicates Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; HR, hazard ratio; NA, not available; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RECOVERY, Randomized Evaluation of COVID-19 Therapy; RR, risk ratio.

[a] Includes only the studies shown that were published in peer-reviewed journals or as preprints.

included because it did not present quantitative results. However, according to their reported preliminary analysis including 912 participants requiring intensive care unit support, treatment with convalescent plasma did not show a beneficial effect on the number of days requiring intensive support or on mortality. The REMAP-CAP preliminary findings are consistent with

our summarized results and, given the relatively small sample size of REMAP-CAP compared with the RECOVERY trial,[8] the data would likely not change our interpretation.

Difficulties in synthesizing evidence across COVID-19 trials because of heterogeneous outcome measures were anticipated by Zarin and Rosenfeld[28] who identified 351 unique descriptions for outcome measures among 232 trials registered until June 2020, including 14 unique ordinal scales. Besides precluding a meaningful overview, unnecessary variation in outcome measures makes precise conclusions more challenging. To aid the development of uniform outcome measurement across trials, core outcome sets involving patients may be a fruitful way forward.[29]

Limitations

This study has several limitations. First, 3 of the 10 RCTs had some concerns or high risk of bias. However, those 3 RCTs only contributed to 1.8% of the weight of the meta-analysis on all-cause mortality, which was highly dominated by data from the RECOVERY trial. Although access to full publication of the results was not yet available, the mortality results from the RECOVERY trial appear likely to be at low risk of bias and without a specific reason to downgrade the certainty of evidence based on previously published treatment group results and the RECOVERY trial protocol.[4-6,26,27]

Second, the reporting of clinical outcomes, other than all-cause mortality, for RECOVERY was insufficient and inconsistent regarding the use of definitions and relevant details across its COVID-19 treatment trials.

Third, the data were too limited to perform meaningful subgroup analyses. The observations reported in the literature regarding a benefit with early high-titer plasma[1] administration in observational studies call for further analyses based on individual patient data such as the Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients (COMPILE) project.[30]

Fourth, except for 1 RCT with outpatients,[16] all patients were hospitalized with or without oxygen supplementation, indicative of moderate to critical COVID-19. The generalizability of the results to patients with milder COVID-19 is unclear.

Fifth, the primary focus of this meta-analysis was on published RCTs. There are many ongoing trials (>100) assessing convalescent plasma that are at risk of being terminated early or never published, but a collaborative meta-analysis of all these data is underway.[31]

Conclusions

Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

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The JAMA Forum

The Coronavirus Pandemic 1 Year On—What Went Wrong?

Lawrence O. Gostin, JD

January 30, 2021, marked the first anniversary of the declaration by the World Health Organization (WHO) of COVID-19 as a public health emergency of international concern (PHEIC). Thus far, the world has been no match for SARS-CoV-2, with more than 100 million cases and 2.5 million deaths. The US has been among the world's poorest performers in addressing the pandemic, with more than 500 000 deaths.

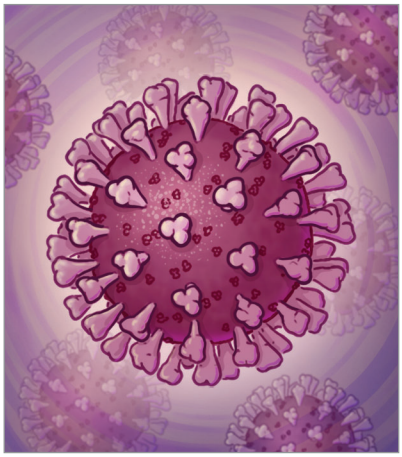
Vaccines offer the best chance of returning to normal, but circulating variants pose a major obstacle, particularly the emergence of variants that are more transmissible and are developing partial resistance to vaccines against SARS-CoV-2. With rampant global circulation, SARS-CoV-2 will have ample opportunity to mutate further.

What went wrong and how can society learn from its greatest failures?

The Collapse of Global Solidarity

At a national level, the lessons are clear, including undervaluing science, weak public health infrastructure, and public resistance to risk mitigation measures like wearing a mask. At the global level, the collective failures have been still greater. By the time the World Health Assembly met in May 2020, the agency was caught in a geopolitical conflict between the US and China. World Health Assembly resolution 73.1 directed the WHO's Director-General to appoint the Independent Panel for Pandemic Preparedness and Response (IPPPR), charged with comprehensively evaluating the international health response, especially the WHO's role. Of particular concern was identifying the zoonotic origins of SARS-CoV-2. The Assembly similarly established the International Health Regulations (IHR) Review Committee to examine the utility of the world's regulations for governing health security.

On January 18, the IPPPR released its second interim report to the WHO's executive board. Just days earlier, on January 13, an expert WHO team finally arrived in Wuhan, China, to study SARS-CoV-2's biological origins. It took the agency more than a year to negotiate the visit with China, jeopardizing the chance to discover the origins of SARS-CoV-2. The WHO concluded on February 9 that the initial outbreak in Wuhan was most likely naturally occurring,



rather than an accidental leak from the Wuhan Institute of Technology, but did give credence to the idea that SARS-CoV-2 originated from an animal shipment from abroad. Even now, there is little transparency as to the scope of the WHO's access to key geographic locations, complete data, and open discussions with Chinese health workers and scientists. The IPPPR's interim report lays bare the failures of the global response, concluding that it would be "unconscionable" to fail to heed the lessons of the pandemic.

Early Failure of the Global Health System

SARS-CoV-2 is a highly transmissible pathogen, fueled by asymptomatic spread. Rapid detection of and response at the Wuhan wet market may not have prevented the pandemic, but it was the world's only opportunity. Yet a timeline of events shows major delays in China's reporting and the veracity of information provided to the WHO. The IPPPR concluded the global alert system and the WHO's power to verify key facts are not "fit for purpose."

Although the earliest cases probably date back to early December 2019, Wuhan hospitals were seeing novel unexplained pneumonias by mid-December. On December 31, 2019, China's National Health Commission finally announced an outbreak of viral pneumonia unrelated to SARS that was "under control" and exhibited no evidence of human-to-human transmission. Yet China did not report the novel viral clusters to the WHO, even though the IHR requires notification within 24 hours. Instead, the WHO was alerted through news and social media outlets. The IHR requires the WHO to confirm nonofficial information with the country of origin, but China did not confirm until January 3, 2020. Due to the lack of accurate and full reporting, the WHO continued to publish inaccurate information regarding human-to-human transmission.

A Better System for Outbreak Detection and Verification

The timeline of events clearly shows the need to empower the WHO to independently verify official reports and to deploy support and containment personnel to member states, including to places where the outbreak originated. Sovereign states will almost certainly resist IPPPR proposals to empower the WHO to enter their territory and gain access to full information. Yet given the unimaginable suffering and economic loss due to the pandemic, strong accountability mechanisms are warranted, including an inspectorate system like the ones currently in nuclear nonproliferation treaties.

Also, when the WHO receives credible outbreak information (regardless of the source), it must be able to act while protecting its source from possible retaliation. The IHR provides only limited confidentiality protection of the data source, which places whistleblowers in potential peril.

An Amply Funded WHO

The world needs a better-resourced WHO. The agency's biannual budget typically ranges between $4 billion and $5 billion

(about that of a large US hospital), with about three-quarters earmarked for specific donor initiatives. Member states should at least double their assessed contributions to the WHO and provide the organization with flexibility to put funding toward the most pressing health threats.

Declaring a PHEIC

The WHO has been criticized for not declaring COVID-19 a global health emergency until January 30, 2020, by which time SARS-CoV-2 had spread to 20 places outside China. Yet with limited information, the agency had valid concerns about stimulating panic and an overreaction, which could dilute the significance of future PHEIC declarations. Contrasted with the rigid, binary nature of current PHEIC determinations, an intermediate level declaration could alert countries of evolving threats.

Coordinated National Responses

Even after the PHEIC had been declared, countries were slow to act. In part because governments failed to build IHR core health system capacities, including surveillance, testing, and contact tracing. Stronger IHR mechanisms to secure funding for and to evaluate health systems would support core capacities, leaving countries far more prepared in the future. National leaders also sought to preserve their economies, though the health-vs-economy dichotomy proved erroneous. Even as the global economy declined by more than $7 trillion, countries that responded aggressively fared far better economically. Countries must learn from experience, both by investing in pandemic preparedness and prioritizing health once an outbreak strikes.

Nowhere was the collapse of global solidarity greater than in the global competition for scarce medical resources. Wealthier nations bought up the world's supplies for personal protective equipment, ventilators, and test kits, creating a global bidding war in which poorer countries could not compete. And although the approval of COVID-19 vaccines before the end of 2020 was a historic achievement, it is clouded by inequitable distribution. High-income countries with their own vaccine supply deals are expected to vaccinate nearly their entire populations by the end of 2021. Lower-income countries (reliant on the COVID-19 Vaccine Global Access Facility) may not accomplish the same until 2 years later, with some estimates projecting the world will not be fully vaccinated for a decade. In addition to being inequitable, it also puts the whole world at greater risk as SARS-CoV-2 will continue to circulate, mutate to evade vaccines, and again spread across the globe. The major disruptions in low- and middle-income countries' health services, including childhood immunizations, will continue to cause excess deaths well beyond COVID-19.

Heeding the Warnings for Future Pandemics

Even after the catastrophic effects of earlier outbreaks of SARS, Ebola virus disease, and Zika virus disease, nations became complacent, failing to prepare domestically or fund global response capabilities. The world largely ignored glaring biological warning signals—but that must not be the case this time. With a pandemic that has touched every life on the globe, has already cost more than 2 million lives, has devastated economies, and will continue to afflict the health of societies for years to come, the calls to reimagine and re-create systems for global health security must not go unheeded. ■

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Correction: This article was corrected on February 16, 2021, to add the fourth sentence to the second paragraph in "The Collapse of Global Solidarity" section.

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