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Item Type	Journal Article
Authors	Guharoy, Roy;Krenzelok, Edward P.
Citation	<p>Guharoy R, Krenzelok EP. FDA Emergency Use Authorization: Glass Half Empty? Clin Infect Dis. 2020 Oct 26:ciaa1653. doi: 10.1093/cid/ciaa1653. Epub ahead of print. PMID: 33104216; PMCID: PMC7665427. <a href="https://doi.org/10.1093/cid/ciaa1653">Link to article on publisher's site</a></p>
DOI	<a href="https://doi.org/10.1093/cid/ciaa1653">10.1093/cid/ciaa1653</a>
Download date	2025-03-21 07:40:31
Link to Item	<a href="https://hdl.handle.net/20.500.14038/41613">https://hdl.handle.net/20.500.14038/41613</a>

# US Food and Drug Administration (FDA) Emergency Use Authorization: Glass Half Full or Glass Half Empty?

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Recently, the US Food and Drug Administration (FDA) issued emergency use authorization (EUA) for convalescent plasma (CP) for the treatment of hospitalized patients with coronavirus disease 2019 based on a non-peer-reviewed, open-label, observational study. Issuance of an EUA without a proven randomized, controlled trial (RCT) sets a dangerous precedent since the premature action drives healthcare providers and patients away from RCTs that are essential for determining the efficacy and safety of CP. More caution should have been taken based on what was learned from the recent debacle related to the rescinded EUA of hydroxychloroquine and chloroquine, which were approved initially based on an anecdotal report. The FDA process for determining efficacy and safety must be based solely on data from RCTs in order to sustain public and professional trust for future treatment and vaccine efforts to be successful.

**Keywords.** emergency use authorization; convalescent plasma; randomized, controlled trial; public trust.

The use of convalescent plasma (CP) for passive immunity against severe acute viral illness spanning from the 1918 Spanish flu to hepatitis A and B, Ebola, severe acute respiratory syndrome, and influenza has worked with varying levels of success [1, 2]. The majority of CP studies were low or very low in quality, lacked control groups, and were at risk of bias. The antibodies from CP are presumed to exert an antiviral effect, preventing virus replication before patients produce their own humoral immune responses [3, 4]. Antibodies can neutralize virus infectivity directly or through Fc-mediated functions [5, 6]. Despite early promising results from anecdotal reports and observational studies for the treatment of severe acute respiratory viral infections, CP failed to demonstrate a benefit for severe influenza A virus infection in randomized, controlled trials (RCTs) [1, 2, 7, 8]. In a recent study, it was reported that some patients not exposed to the coronavirus disease 2019 (COVID-19) virus already had T cells against the virus in their system [9]. This may explain how previous exposure to coronaviruses provide a head start on fighting the new virus.

On 23 August 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for CP for the treatment of hospitalized patients with COVID-19 based on a non-peer-reviewed report [10, 11]. An open-label, observational, multicenter study with 35 322 transfused patients

conducted by the Mayo Clinic revealed that the 7-day mortality rate was 8.7% (95% confidence interval [CI], 8.3%–9.2%) in patients who were transfused within 3 days of a COVID-19 diagnosis and 11.9% (95% CI, 11.4%–12.2%) if transfused 4 or more days after diagnosis ( $P < .001$ ) [11]. Similar findings were observed in 30-day mortality (21.6% vs 26.7%,  $P < .0001$ ). For patients who received high immunoglobulin (Ig) G plasma ( $>18.45$  signal-to-cutoff [S/Co] ratio), the 7-day mortality rate was 8.9% (95% CI, 6.8%–11.7%), 11.6% for those on medium IgG plasma (4.62–18.45 S/Co ratio; 95% CI, 10.3%–13.1%), and 13.7% for recipients of low IgG plasma ( $<4.62$  S/Co ratio; 95% CI, 11.1%–16.8%;  $P = .048$ ). The pooled relative risk of mortality among patients who received high IgG plasma was 0.65 (95% CI, .47–.92) for 7 days and 0.77 (95% CI, .63–.94) for 30 days vs those on low IgG plasma. Overall mortality was lower in patients who received CP within 3 days of diagnosis vs  $\geq 4$  days post diagnosis. Although reduced mortality rate is a positive sign, no definitive conclusion can be drawn since there was no comparison with a control group to demonstrate that the treatment worked. Most of the patients also received other treatments, including antibiotics, antivirals, antifungals, corticosteroids, and hydroxychloroquine (HCQ). The original intent of the trial was to determine the safe use of CP, not its efficacy [12]. As is common with observational trials, there were multiple issues with the study design, including selection bias, comparison with a control group on standard of care or concomitant use of other treatments, and comparison with the same cohort such as those who receive early vs late CP. There may be confounding variables where those who received CP early were treated more aggressively than those who received it late.

Received 2 September 2020; editorial decision 22 October 2020; published online 26 October 2020.

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**Clinical Infectious Diseases**® 2020;XX(XX):1–4

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DOI: 10.1093/cid/ciaa1653

The FDA determined that CP “may be effective” and eligible for an EUA after analysis of 4330 patients from the Mayo Clinic data demonstrated no difference in 7-day mortality among patients who received high-IgG titer vs low-IgG titer plasma in the overall population or in the subset of intubated patients [10, 13, 14]. Among the nonintubated patients, death occurred within 7 days of transfusion in 11% of patients in the high-titer plasma group vs 14% in the low-titer plasma group ( $P = .03$ ) [13, 14]. The 7-day mortality in nonintubated patients who were aged <80 years and treated within 72 hours of diagnosis was 6.3% in the high-titer group vs 11.3% in the low-titer group ( $P = .0008$ ). While the EUA meets “may be effective” criteria, the analysis did not appear to establish the efficacy or safety of CP because of the lack of comparison with a control group.

There were only 2 underpowered, unblinded RCT reports with a total of 189 hospitalized patients, of whom 95 patients received CP at the time of the EUA approval [15, 16]. In an open-label RCT of 103 patients with severe and life-threatening COVID-19 stratified by disease severity, 52 patients received CP and standard treatment and 51 patients received standard treatment [15]. There was no statistically significant difference in the primary outcome of clinical improvement within 28 days where 51.9% of the CP recipients had clinical improvement vs 43.1% in the control group (hazard ratio [HR], 1.40; 95% CI, .79–2.49;  $P = .26$ ). Secondary outcomes did not demonstrate any significant difference between 2 groups in terms of 28-day mortality (15.7% vs 24.0%; HR 0.59; 95% CI, .22–1.59;  $P = .30$ ) and the time from randomization to discharge (51% vs 36.0% discharged by day 28; HR 1.61; 95% CI, .88–2.95;  $P = .12$ ). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care. The trial was terminated early because of low enrollment secondary to containment of the epidemic at study locations.

Another RCT (non-peer-reviewed) compared 43 patients on CP and standard care with the same number of patients on standard care alone [16]. There were no differences in mortality (adjusted OR [aOR], 0.95; 95% CI, .20–4.67;  $P = .95$ ), day-15 disease severity (aOR, 1.30; 95% CI, .52–3.33;  $P = .58$ ), or hospital length of stay (aOR, 0.88; 95% CI, .49–1.60;  $P = .68$ ) observed between plasma-treated patients and those on standard of care. No serious adverse events were reported. The study was halted because of concerns about lack of benefit. In addition, the majority of patients already had high titers of virus-neutralizing antibodies at baseline. Interestingly, this may shine light as to why CP failed for the treatment of Ebola [17, 18]. Future studies should consider testing patients for antibody titers prior to treatment with CP.

To date, 2 other RCTs have been identified (non-peer-reviewed) [19, 20]. The only completed RCT is an open-label, parallel-arm, phase 2 trial PLACID-PLAsma Convalescent InDia (PLACID) in patients with moderate COVID-19 where 235 patients were enrolled in the intervention group and 229

in the control group to assess composite outcome of progression to severity or all-cause mortality at 28 days [19]. Overall, CP did not improve either of the trial outcomes. The composite primary end point, that is, progression to severe disease, was achieved in 19% of patients in the intervention group vs 18% in the control group (RR, 1.05; 95% CI, .71–1.54); 15% of deaths occurred in the intervention group vs 14% in the control group (RR 1.04; 95% C, .66–1.63). CP titers used in the study were low.

The other underpowered open-label RCT with 81 patients assessed the efficacy and safety of CP in preventing progression to severe disease or death in hospitalized patients with early COVID-19 (non-peer-reviewed) [20]. The study was stopped early because of low enrollment. A total of 38 patients assigned to receive CP had a lower rate of worsening at 15 days compared with 43 patients on standard of care. There were no deaths or progression to the need for mechanical ventilation in the CP group compared with 6 patients in the control group. Mortality rates were 0% vs 9.3% at days 15 and 29 for the CP and control groups. Six serious adverse events were reported in the CP group vs 7 in the control group. Similar to the other 2 underpowered RCTs, it is difficult to conclude whether CP was beneficial or not.

Serious adverse events such as lung damage, anaphylaxis, and immune reactions are associated with CP use [21]. The Mayo Clinic study, which was considered for the EUA, reported 868 serious adverse events among 20 000 patients [12]: 78 patients had transfusion reactions (<1%), 113 patients had thrombotic or thromboembolic events (<1%), and 677 patients had cardiac events (approximately 3%). In total, 96% of thrombotic or thromboembolic and 88% of cardiac events were deemed to be unrelated to transfusion. The 7-day mortality rate was 13.0% (95% CI, 12.5%–13.4%). It was higher among patients who were critically ill relative to less ill patients, including patients admitted to the intensive care unit vs those not admitted (15.6 vs 9.3%), patients mechanically ventilated vs not mechanically ventilated (18.3% vs 9.9%), and patients with septic shock or multiple organ dysfunction/failure vs those without dysfunction/failure (21.7% vs 11.5%).

A recent updated Cochrane systematic review of 19 published trials with 36 081 hospitalized patients concluded that “efficacy and safety benefits of CP cannot be determined in the absence of comparison against control group” [22]. The recent National Institutes of Health updated guidelines for the treatment of COVID-19 concluded that “there are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 CP for the treatment of COVID-19” [23, 24]. The Infectious Diseases Society of America issued guidelines for managing COVID-19 that recommended the use of CP in the context of a controlled trial [25]. The chief scientist of the World Health Organization stated that current data on CP are inconclusive, lack quality evidence, and should be evaluated in well-designed randomized, controlled trial [26].

This is the second time in just 7 months that the FDA's decision-making has come into question. The EUA regarding HCQ, issued on 28 March 2020, was based solely on an anecdotal report [27, 28]. The authorization resulted in confusion that prompted many health systems to include HCQ in their treatment protocols. After numerous reports of adverse events and lack of meaningful benefit, the FDA was forced to withdraw the EUA on 15 June 2020 [29]. It is worth noting that the FDA authorized an EUA during the 2009–2010 swine flu outbreak to allow the use of peramivir, an investigational agent, in 1200 to 1500 severely ill hospitalized patients with H1N1 influenza. Later, the FDA approved peramivir for treatment of uncomplicated influenza after a randomized, clinical trial failed to show any benefit of peramivir use in severely ill hospitalized patients [30].

Issuance of an EUA without proven clinical efficacy establishes a questionable precedent since the premature authorization may drive healthcare providers and patients away from participating in properly designed RCTs that are essential for determining the efficacy and safety of CP. While lack of access to RCTs at many hospitals during the pandemic is a challenge, a balance between availability and scientific evidence of safety and effectiveness of promising therapies is imperative in ensuring that clinicians are not deprived of the compassionate use of CP outside of a RCT. Under the current Federal Food, Drug and Cosmetic Act, patients with serious or immediately life-threatening diseases or conditions are permitted access to investigational drugs outside of clinical trials [31].

Premature HCQ and CP use without evidence was a missed opportunity. The pandemic, which has affected more than 9.3 million people in the United States and 48 million people worldwide (as of 5 November 2020), offers the unique opportunity to perform RCTs that are complete, prospective, adequately powered, and rigorous within a very short time [32, 33]. The RECOVERY (Randomized Evaluation of COVID-19 Therapy), ACTT (Adaptive COVID-19 Treatment Trial), and the World Health Organization international clinical trial (WHO-SOLIDARITY) trials have taught us that well-controlled, adequately powered RCTs are possible during the challenges of the pandemic [34–36].

The FDA's repeated failure to adhere to scientific rigor has compromised the agency's reputation for independence and science at a critical time when we are facing the most severe public health crisis of contemporary history. The FDA's credibility is critical to ensure public confidence that key decisions are made independently and based on science. Despite years of public education and clinician efforts, vaccine hesitancy remains a major problem in the United States. Only 45.6% of adults and 62.6% of individuals aged 6 months–17 years were vaccinated against influenza during the 2018–2019 season [37]. Due to the highly contagious nature of the virus, a high level of compliance with COVID-19 vaccines when they become available is absolutely

necessary to “flatten the curve.” A recent Pew research poll among 10 093 adults in September found that only 21% would be vaccinated if a vaccine were available immediately compared with 42% in a similar poll in May [38]. The implications of such failing trust during the middle of a pandemic are concerning.

Public trust in the FDA's mission to approve safe and effective medications was built by the highly capable scientists of the FDA over the years. Moving forward, the FDA needs to establish a clear, transparent, and rigorous scientific process for future emergent therapies in order to maintain scientific integrity and sustain public trust. The decisions should be based on evidence from well-controlled, adequately powered RCTs and input from both internal and external subject matter experts. The data should be available to both the public and clinicians throughout the process. The new process also needs to include specific terms for adequate monitoring and reporting of safety and outcomes by the providers in order to achieve robust post-EUA surveillance. Such improvements will help the FDA to meet its mission of delivering safe and effective access to lifesaving products during public health crises.

The FDA approval process for determining efficacy and safety must be based solely on data from RCTs. Anything else has the potential to erode the trust of the public and thus would be a public health tragedy. If we have learned anything from the pandemic, it is that we need public and professional trust for future treatment and vaccine efforts to be successful. The only exception to RCT-based evidence should be compassionate use when deemed absolutely necessary.

## Notes

**Disclaimer.** The opinions expressed in this article are those of the authors and do not purport the opinions or views of their affiliated organizations.

**Potential conflicts of interest.** The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

## References

- Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al; Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* **2015**; 211:80–90.
- Subbarao K, Mordant F, Rudraraju R. Convalescent plasma treatment for COVID-19: tempering expectations with the influenza experience. *Eur J Immunol* **2020**; 50:1447–53.
- Rojas M, Rodríguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: possible mechanisms of action. *Autoimmun Rev* **2020**; 19:102554.
- Sharun K, Tiwari R, Iqbal Yattoo M, et al. Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects. *Expert Opin Biol Ther* **2020**; 20:1033–46.
- Gunn BM, Yu WH, Karim MM, et al. A role for Fc function in therapeutic monoclonal antibody-mediated protection against Ebola virus. *Cell Host Microbe* **2018**; 174: 221–33.
- Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* **2020**; 130:2757–65.
- Beigel JH, Tebas P, Elie-Turenne MC, et al; IRC002 Study Team. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med* **2017**; 5:500–11.
- Beigel JH, Aga E, Elie-Turenne MC, et al; IRC005 Study Team. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. *Lancet Respir Med* **2019**; 7:941–50.



9. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Sci Immunol* **2020**; 48. doi: [10.1126/sciimmunol.abd2071](https://doi.org/10.1126/sciimmunol.abd2071).
10. US Food and Drug Administration. Convalescent plasma EUA fact sheet for health care providers. 23 August 2020. Available at: <https://www.fda.gov/media/141478/download>. Accessed 25 August 2020.
11. Joyner MJ, Seneff JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *MedRxiv* 20169359 [Preprint - non peer reviewed] August 12, 2020. doi: [10.1101/2020.08.12.20169359](https://doi.org/10.1101/2020.08.12.20169359). Available from: <https://doi.org/10.1101/2020.08.12.20169359>. Accessed 25 August 2020.
12. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* **2020**; 95:1888–97.
13. US Food and Drug Administration. Clinical memorandum: COVID-19 convalescent plasma. 2020. Available at: <https://www.fda.gov/media/141480/download>. Accessed 15 October 2020.
14. US Food and Drug Administration. EUA 26382: emergency use authorization (EUA). Available at: <https://www.fda.gov/media/141481/download>. Accessed 15 October 2020.
15. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* **2020**; 324:460–70.
16. Gharbharan A, Jordans CC, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19. A randomized clinical trial. *medRxiv* 20139857 [Preprint - non peer reviewed]. July 3, 2020. doi: [10.1101/2020.07.01.20139857](https://doi.org/10.1101/2020.07.01.20139857). Available at: <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1.full.pdf>. Accessed 26 August 2020.
17. van Griensven J, Edwards T, de Lamballerie X, et al; Ebola-Tx Consortium. Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N Engl J Med* **2016**; 374:33–42.
18. Sahr F, Ansumana R, Massaquoi TA, et al. Evaluation of convalescent whole blood treating Ebola virus disease in Freetown, Sierra Leone. *J Infect* **2017**; 74: 302–9.
19. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of COVID-19 in India: an open label phase II multicenter randomized controlled trial (PLACID trial). *BMJ* **2020**; 371:m3939. Available at: <https://www.bmj.com/content/371/bmj.m3939>. Accessed 3 November 2020.
20. Avendano-Sola A, Ramos-Martinez A, Munoz-Rubio E. Convalescent plasma for COVID-19: a multicenter randomized control trial. *medRxiv* [Preprint - non peer reviewed]. September 29, 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v3.full.pdf>. Accessed 17 October 2020.
21. Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion* **2012**; 52(Suppl 1):65S–79S.
22. Chai KL, Valk SJ, Piechotta V, et al. Convalescent plasma or hyperimmunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev* **2020**. 12 October 2020. Available at: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013600.pub3/full>. Accessed 4 November 2020.
23. National Institutes of Health. COVID-19 treatment guidelines. 9 October 2020. Available at: <https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma>. Accessed 15 October 2020.
24. Pau AK, Aberg J, Belperio PS, et al. Convalescent plasma for the treatment of COVID-19; perspectives of the National Institutes of Health COVID-19 treatment panel. *Ann Int Med* **2020**. doi: [10.7326/M20-6448](https://doi.org/10.7326/M20-6448). Available at: <https://www.acpjournals.org/doi/10.7326/M20-6448>. Accessed 18 October 2020.
25. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis* **2020**. Available at: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management>. Accessed 15 October 2020.
26. Cheng M. UN cautions viral plasma is still experimental. *Washington Post*. August 24, 2020. Available at: [https://www.washingtonpost.com/world/europe/un-cautions-that-virus-plasma-treatment-still-experimental/2020/08/24/1749fa74-e630-11ea-bf44-0d31c85838a5\\_story.html](https://www.washingtonpost.com/world/europe/un-cautions-that-virus-plasma-treatment-still-experimental/2020/08/24/1749fa74-e630-11ea-bf44-0d31c85838a5_story.html). Accessed 3 November 2020.
27. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. *Int J Antimicrob Agents* **2020**;105949. Available at: <https://www.sciencedirect.com/science/article/pii/S0924857920300996>. Accessed 24 August 2020.
28. US Food and Drug Administration. Request for emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 coronavirus disease. 28 March 2020. Available at: <https://www.fda.gov/media/136534/download>. Accessed 20 August 2020.
29. US Food and Drug Administration. Coronavirus update (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. 15 June 2020. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and>. Accessed 20 August 2020.
30. Pavia AT. Editorial commentary: what did we learn from the emergency use authorization of peramivir in 2009. *Clin Infect Dis* **2012**; 55:16–8.
31. US Food and Drug Administration. Expanded access (current as of 27 April 2020). Available at: <https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians>. Accessed 5 November 2020.
32. Centers for Disease Control and Prevention. Cases in the U.S. —coronavirus disease 2019 (COVID-19). Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>. Accessed 5 November 2020.
33. Johns Hopkins University. Maps and trends: mortality analyses. Johns Hopkins University & Medicine Coronavirus Resource Center website. Available at: <https://coronavirus.jhu.edu/data/mortality>. Accessed 5 November 2020.
34. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19: interim WHO SOLIDARITY trial results. *medRxiv* [Preprint - non peer reviewed]. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1>. Accessed 16 October 2020.
35. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of COVID-19— final report. *N Engl J Med* **2020**. doi: [10.1056/NEJMoa2007764](https://doi.org/10.1056/NEJMoa2007764). Available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2007764>. Accessed 15 October 2020.
36. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* **2020**. doi: [10.1056/NEJMoa2021436](https://doi.org/10.1056/NEJMoa2021436). Available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2021436>. Accessed 15 October 2020.
37. Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2018–19 flu season. Available at: <https://www.cdc.gov/flu/fluavxw/cvcoverage-1819estimates.htm>. Accessed 26 August 2020.
38. Tyson A, Johnson C, Funk C. U.S. public now divided over whether to get COVID-19 vaccine. *Pew Research Center*. 17 September 2020. Available at: [https://www.pewresearch.org/science/2020/09/17/u-s-public-now-divided-over-whether-to-get-covid-19-vaccine/ps\\_2020-09-17\\_covid-19-vaccine\\_featured](https://www.pewresearch.org/science/2020/09/17/u-s-public-now-divided-over-whether-to-get-covid-19-vaccine/ps_2020-09-17_covid-19-vaccine_featured). Accessed 14 October 2020.