Safety of COVID-19 Therapies and Vaccines

Kenneth L. Hastings, Dr.P.H., D.A.B.T., Fellow A.T.S.
Hastings Toxicology Consulting LLC
Mount Airy, MD 21771
Kennethhastings@gmail.com

June 21, 2022
Epidemiology of COVID-19 Outbreak on Cruise Ship Quarantined at Yokohama, Japan, February 2020

Appendix

![Graph showing the number of febrile patients by date of fever onset for crew and passengers.](https://doi.org/10.3201/eid2611.201165)
Appendix Figure 2. Proportion of fatal, severe, mild, and asymptomatic cases among a population in which all persons were tested by rRT-PCR for SARS-CoV-2. Because the entire population on board the cruise ship was tested with rRT-PCR for SARS-CoV-2, it was possible to illustrate these proportions.

Article DOI: https://doi.org/10.3201/eid2611.201165
Excess All-Cause Deaths during Coronavirus Disease Pandemic, Japan, January–May 2020

Takayuki Kawashima, Shuhei Nomura, Yuta Tanoue, Daisuke Yoneoka, Akitumi Eguchi, Chris Fook Sheng Ng, Kentaro Matsuura, Shoii Shi, Koji Makiyama, Shinya Uryu, Yumi Kawamura, Shinichi Takayanagi, Stuart Gilmore, Hiroaki Miyata, Tomimasa Sunagawa, Takuri Takahashi, Yuuki Tsuchihashi, Yusuke Kobayashi, Yuzo Arima, Kazuhiko Kanou, Motoi Suzuki, Masahiro Hashizume

To provide insight into the mortality burden of coronavirus disease (COVID-19) in Japan, we estimated the excess all-cause deaths for each week during the pandemic, January–May 2020, by prefecture and age group. We applied quasi-Poisson regression models to vital statistics data. Excess deaths were expressed as the range of differences between the observed and expected number of all-cause deaths and the 95% upper bound of the 1-sided prediction interval. A total of 208–4,322 all-cause excess deaths at the national level indicated a 0.03%–0.72% excess in the observed number of deaths. Prefecture and age structure consistency between the reported COVID-19 deaths and our estimates was weak, suggesting the need to use cause-specific analyses to distinguish between direct and indirect consequences of COVID-19.
60,000 more people died of COVID-19 during 2021 compared with 2020; COVID-19 remained the 3rd leading cause of death

PROVISIONAL 2021 DEATHS

1. Heart Disease 693k
2. All causes 605k
3. COVID-19 415k

*Provisional data from CDC’s NCHS, death certificate data analyzing cause of death among US residents in the United States during January-December 2021

NEWS 05 May 2022

15 million people have died in the pandemic, WHO says

The World Health Organization’s long-awaited estimate of excess COVID deaths is in line with other studies
Therapeutic Interventions

• Vaccines – prophylaxis
• Anti-viral Drugs – direct anti-pathogen therapy
• Anti-inflammatory Agents – drugs or biologics
• Convalescent Plasma – passive immunotherapy
• Monoclonal Antibodies – target viral antigens
B. Toxicity Studies (Refs. 10-14)

- For a COVID-19 vaccine candidate consisting of a novel product type and for which no prior nonclinical and clinical data are available, nonclinical safety studies will be required prior to proceeding to FIH clinical trials 21 CFR 312.23(a)(8).
Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

In some cases, it may not be necessary to perform nonclinical safety studies prior to FIH clinical trials because adequate information to characterize product safety may be available from other sources. For example, if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture a licensed vaccine or other previously studied investigational vaccines and is sufficiently characterized, it may be possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for that COVID-19 vaccine candidate. Vaccine manufacturers should summarize the findings and provide a rationale if considering using these data in lieu of performing nonclinical safety studies.
Emergency Use Authorization for Vaccines to Prevent COVID-19

Guidance for Industry


This document supersedes the guidance of the same title issued on February 22, 2021 and October 2020.

2. Nonclinical:

   a. A list of the nonclinical studies conducted to support vaccine effectiveness and safety (e.g., characterization of markers associated with enhanced disease, biodistribution, shedding, and attenuation) should be provided, along with the timelines for study completion and submission of final study reports for all ongoing nonclinical studies as applicable.

   b. A final study report, if available, for a Developmental and Reproductive Toxicology (DART) study, or the timeline for study completion and submission of the final study report, should be provided in order to inform potential emergency use of the vaccine in pregnant women.
Safety and Immunogenicity of Two RNA Covid-19 Vaccine Candidates

PHASE 1 PLACEBO-CONTROLLED, OBSERVER-BLINDED, DOSE-ESCALATION TRIAL

195 Healthy adults 18–55 yr and 65–85 yr

13 groups of 15 participants each (12 received vaccine, 3 placebo)

BNT162b1
(Encodes a secreted trimerized SARS-CoV-2 receptor-binding domain)
(N=105)

BNT162b2
(Encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in prefusion conformation)
(N=90)

Safety (primary outcome)

Fever after second dose (temperature ≥38°C)

18–55 yr 65–85 yr 18–55 yr 65–85 yr

75% 33% 17% 8%

Both candidates elicited similar dose-dependent SARS-CoV-2 neutralizing GMTs

Data support advancement of BNT162b2 to phase 2–3 safety and efficacy evaluation

E.E. Walsh et al. 10.1056/NEJMoa2027906

Copyright © 2020 Massachusetts Medical Society
FDA NEWS RELEASE


Action Follows Thorough Evaluation of Available Safety, Effectiveness, and Manufacturing Quality Information by FDA Career Scientists, Input from Independent Experts

For Immediate Release:
December 18, 2020

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the second vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergency use authorization allows the Moderna COVID-19 Vaccine to be distributed in the U.S. for use in individuals 18 years of age and older.
Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents

Barbara H. Bardenheier a,*, Stefan Gravenstein a,b,c, Carolyn Blackman d, Roee Gutman a, Indra Neil Sarkar a,b,e, Richard A. Feifer d, Elizabeth M. White a, Kevin McConeghy a,c, Aman Nanda b, Vincent Mor a,c

Conclusions: No major safety problems were detected following the first or second dose of the vaccine to prevent COVID-19 in the study cohort from December 18, 2020 through March 7, 2021.
Antibodies elicited by mRNA-1273 vaccination bind more broadly to the receptor binding domain than do those from SARS-CoV-2 infection

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with mutations in key antibody epitopes has raised concerns that antigenic evolution could erode adaptive immunity elicited by prior infection or vaccination. The susceptibility of immunity to viral evolution is shaped in part by the breadth of epitopes targeted by antibodies elicited by vaccination or natural infection. To investigate how human antibody responses to vaccines are influenced by viral mutations, we used deep mutational scanning to compare the specificity of polyclonal antibodies elicited by either two doses of the mRNA-1273 COVID-19 vaccine or natural infection with SARS-CoV-2. The neutralizing activity of vaccine-elicited antibodies was more targeted to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein compared to antibodies elicited by natural infection. However, within the RBD, binding of vaccine-elicited antibodies was more broadly distributed across epitopes compared to infection-elicited antibodies. This greater binding breadth means that single RBD mutations have less impact on neutralization by vaccine sera compared to convalescent sera. Therefore, antibody immunity acquired by natural infection or different modes of vaccination may have a differing susceptibility to erosion by SARS-CoV-2 evolution.
Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study

Jamie Lopez Bernal,¹ ² ³ Nick Andrews,¹ ² Charlotte Gower,¹ Chris Robertson,⁴ Julia Stowe,¹ Elise Tessier,¹ Ruth Simmons,¹ Simon Cottrell,⁵ Richard Roberts,⁵ Mark O'Doherty,⁶ Kevin Brown,¹ Claire Cameron,⁷ Diane Stockton,⁷ Jim McMenamin,⁷ Mary Ramsay¹ ²

WHAT THIS STUDY ADDS
A single dose of either BNT162b2 or ChAdOx1-S provides significant protection against covid-19 and further protection against severe disease lasting at least six weeks, including against the UK variant of concern (B.1.1.7)
BNT162b2 and ChAdOx1-S offer similar levels of protection in adults aged 70 and older

Cite this as: BMJ 2021;373:n1088
http://doi.org/10.1136/bmj.n1088
Early effectiveness of COVID-19 vaccination
BNT162b2 mRNA and ChAdOx1-S adenovirus vector vaccines

Summary
One dose of either vaccine provides 60-70% protection against symptomatic COVID-19 and about 80% protection against hospital admission.

Study design
Test negative case-control
Included whole population of over 70s in England (approx. 7.5 million)

Population
153,441 individuals developed symptoms and were tested through community testing (8 Dec to 19 Feb 2021)

Outcomes
- BNT162b2 (Pfizer-BioNTech)
- ChAdOx1-S (Oxford-AstraZeneca)

Symptomatic COVID-19 disease
Adjusted odds ratio for confirmed case by interval after vaccination dose 1, administered from 4 January 2021

Single dose BNT162b2: Vaccine effectiveness reached 61% from 28-34 days after vaccination, then plateaued.

Single dose ChAdOx1-S: Vaccine effectiveness reached 60% from 28-34 days with further increases to 73% from 35 days onwards.


© 2021 BMJ Publishing Group Ltd.
CONCLUSION AND RELEVANCE  In this exploratory analysis of a convenience sample, receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.
US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021

Isaac See, MD; John R. Su, MD, PhD, MPH; Allison Lale, MD, MPH; Emily Jane Woo, MD, MPH; Alice Y. Guh, MD, MPH; Tom T. Shimabukuro, MD, MPH, MBA; Michael B. Streiff, MD; Agami K. Rao, MD; Allison P. Wheeler, MD, MSc; Suzanne F. Beavers, MD; Anna P. Durbin, MD; Kathryn Edwards, MD; Elaine Miller, RN, MPH; Theresa A. Harrington, MD, MPH; Adamma Mba Jonas, MD, MPH; Narayan Nair, MD; Duong T. Nguyen, DO; Kawsar R. Talaat, MD; Victor C. Urrutia, MD; Shannon C. Walker, MD; C. Buddy Creech, MD; Thomas A. Clark, MD, MPH; Frank DeStefano, MD, MPH; Karen R. Broder, MD

CONCLUSIONS AND RELEVANCE The initial 12 US cases of CVST with thrombocytopenia after Ad26.COV2.S vaccination represent serious events. This case series may inform clinical guidance as Ad26.COV2.S vaccination resumes in the US as well as investigations into the potential relationship between Ad26.COV2.S vaccine and CVST with thrombocytopenia.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence rate*</th>
<th>Observed†</th>
<th>Expected</th>
<th>Standardised morbidity difference‡ /100 000 (95% CI)</th>
<th>Standardised morbidity ratio (95% CI)</th>
<th>Standardised morbidity ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia/coagulation disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.60/0.75</td>
<td>24</td>
<td>16</td>
<td>3.0 (-0.2 to 7.4)</td>
<td>1.52 (0.97 to 2.25)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>0.07/0.06</td>
<td>n&lt;5</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Other primary thrombocytopenia</td>
<td>0.00/0.01</td>
<td>0</td>
<td>0.1</td>
<td>-0.0 (-0.0 to 1.3)</td>
<td>0.00 (0.00 to 35.70)</td>
<td></td>
</tr>
<tr>
<td>Secondary thrombocytopenia</td>
<td>0.01/0.18</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia unspecified</td>
<td>0.09/0.20</td>
<td>11</td>
<td>3</td>
<td>2.9 (0.9 to 6.1)</td>
<td>3.57 (1.78 to 6.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation disorders, purpura</td>
<td>0.45/0.38</td>
<td>7</td>
<td>10</td>
<td>-1.3 (-2.8 to 1.5)</td>
<td>0.67 (0.27 to 1.39)</td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>0.01/0.02</td>
<td>0</td>
<td>0.3</td>
<td>-0.1 (-0.1 to 1.3)</td>
<td>0.00 (0.00 to 12.20)</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia from bleeding</td>
<td>0.11/0.60</td>
<td>n&lt;5</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Bleeding from respiratory tract</td>
<td>0.85/0.87</td>
<td>35</td>
<td>16</td>
<td>7.1 (3.2 to 12.2)</td>
<td>2.21 (1.54 to 3.08)</td>
<td></td>
</tr>
<tr>
<td>Bleeding, not specified</td>
<td>0.15/0.05</td>
<td>8</td>
<td>2</td>
<td>2.1 (0.4 to 4.9)</td>
<td>3.30 (1.42 to 6.50)</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>1.43/1.50</td>
<td>25</td>
<td>31</td>
<td>-2.1 (-5.4 to 2.3)</td>
<td>0.81 (0.53 to 1.20)</td>
<td></td>
</tr>
<tr>
<td>Intestinal bleeding</td>
<td>0.18/-§</td>
<td>n&lt;5</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Haemolytic anaemias¶</strong></td>
<td>0.09/0.09</td>
<td>0</td>
<td>2</td>
<td>-0.8 (-0.8 to 0.5)</td>
<td>0.00 (0.00 to 1.66)</td>
<td></td>
</tr>
</tbody>
</table>
Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

Anton Pottegård,1 Lars Christian Lund,1 Øystein Karlstad,2 Jesper Dahl,2 Morten Andersen,3 Jesper Hallas,1 Øjvind Lidegaard,4,5 German Tapia,2 Hanne Løvdal Gulseth,2 Paz Lopez-Doriga Ruiz,2 Sara Viksmoen Watle,3 Anders Pretzmann Mikkelsen,4,5 Lars Pedersen,6,7 Henrik Toft Sørensen,6,7 Reimar Wernich Thomsen,6,7 Anders Hviid3,8

WHAT THIS STUDY ADDS
Increased rates for venous thromboembolism were observed within 28 days of vaccination with ChAdOx1-S in Denmark and Norway, corresponding to 11 excess events per 100 000 vaccinations, including 2.5 excess cerebral venous thrombosis events per 100 000 vaccinations.

Results were largely reassuring for arterial events, whereas slightly increased rates of thrombocytopenia or coagulation disorders and bleeding in the vaccinated group could be influenced by heightened surveillance.

Absolute risks of events were small and should be interpreted in the context of the benefits of covid-19 vaccination at both the societal and the individual level.
Thrombotic thrombocytopenia associated with COVID-19 infection or vaccination: Possible paths to platelet factor 4 autoimmunity

Michel Goldman¹*, Cédric Hermans²

¹ Institute for Interdisciplinary Innovation in Healthcare, Université libre de Bruxelles (ULB), Brussels, Belgium, ² Division of Hematology, Hemostasis and Thrombosis Unit, Saint-Luc University Hospital, Université catholique de Louvain (UCLouvain), Brussels, Belgium
Fig 1. Hypothetical model for thrombotic thrombocytopenia during COVID-19. (A) SARS-CoV-2 induces the release of PF4 by activated platelets and of polyanionic PG by endothelial cells (e.g., syndecan and endocan). (B) Complexes of PF4 and PG expose PF4 immunogenic epitopes, which activate extrafollicular B lymphocytes secreting PF4 autoantibodies. (C) PF4 autoantibodies bind complexes of PF4 and PG on platelets and endothelial cells and stimulate their procoagulant activities. Cross-linking of FcγRIIA receptors also promote apoptosis and clearance of antibody-decorated platelets. COVID-19, Coronavirus Disease 2019; PF4, platelet factor 4; PG, proteoglycan; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.
CONCLUSIONS AND RELEVANCE In this case-control analysis, no association was found between recent vaccination with the BNT162b2 vaccine and risk of facial nerve palsy.

IMPORTANTANCE Peripheral facial nerve (Bell) palsy has been reported and widely suggested as a possible adverse effect of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine. Israel is currently the leading country in vaccination rates per capita, exclusively using the BNT162b2 vaccine, and all residents of Israel are obligatory members of a national digital health registry system. These factors enable early analysis of adverse events.

Published online June 24, 2021.
RESEARCH LETTER Incidence of Bell Palsy in Patients With COVID-19

The present analysis found a higher incidence of BP in patients with COVID-19 (0.08%). This translates to approximately 82 per 100,000 patients with COVID-19. The rate of recurrent BP in patients with previous BP at the time of COVID-19 diagnosis was 8.6%. This analysis found a statistically significant higher risk of BP in patients with COVID-19 compared with those who were vaccinated against the disease. The data suggest that rates of BP are higher in patients with COVID-19, and this incidence exceeds the reported incidence of BP in those who have received a COVID-19 vaccine.

Emily Jane Woo, MD, MPH; Adamma Mba-Jonas, MD, MPH; Rositsa B. Dimova, PhD; Meghna Alimchandani, MD; Craig E. Zinderman, MD, MPH; Narayan Nair, MD

CONCLUSIONS AND RELEVANCE These findings suggest a potential small but statistically significant safety concern for Guillain-Barré syndrome following receipt of the Ad26.COV2.S vaccine. However, the findings are subject to the limitations of passive reporting systems and presumptive case definition, and they must be considered preliminary pending analysis of medical records to establish a definitive diagnosis.

Published online October 7, 2021.
CONCLUSIONS AND RELEVANCE  In this cohort study of COVID-19 vaccines, the incidence of GBS was elevated after receiving the Ad.26.COV2.S vaccine. Surveillance is ongoing.

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel


CONCLUSIONS
The incidence of myocarditis, although low, increased after the receipt of the BNT162b2 vaccine, particularly after the second dose among young male recipients. The clinical presentation of myocarditis after vaccination was usually mild.
Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination — PCORnet, United States, January 2021–January 2022

Jason P. Block, MD1; Tegan K. Boehmer, PhD2; Christopher B. Forrest, MD, PhD3; Thomas W. Carton, PhD4; Grace M. Lee, MD5; Umed A. Ajani, MBBS2; Dimitri A. Christakis, MD6; Lindsay G. Cowell, PhD7; Christine Draper1; Nidhi Ghildayal, PhD1; Aaron M. Harris, MD2; Michael D. Kappelman, MD8; Jean Y. Ko, PhD2; Kenneth H. Mayer, MD9; Kshema Nagavedu, MPH1; Matthew E. Oster, MD2,10; Anuradha Paranjape, MD11; Jon Puro, MPA12; Matthew D. Ritchey2; David K. Shay, MD2; Deepika Thacker, MD13; Adi V. Gundlapalli, MD, PhD2

Summary

What is already known about this topic?

Studies have found an increased risk for cardiac complications after SARS-CoV-2 infection and mRNA COVID-19 vaccination, but few have compared these risks.

What is added by this report?

Data from 40 health care systems participating in a large network found that the risk for cardiac complications was significantly higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination for both males and females in all age groups.

What are the implications for public health practice?

These findings support continued use of recommended mRNA COVID-19 vaccines among all eligible persons aged ≥5 years.
Delayed Localized Hypersensitivity Reactions to the Moderna COVID-19 Vaccine: A Case Series

Margaret S. Johnston, MD; Anjela Galan, MD; Kalman L. Watsky, MD; Alicia J. Little, MD, PhD

CONCLUSIONS AND RELEVANCE Clinical and histopathologic findings of this case series study indicate that the localized injection-site reactions to the Moderna COVID-19 vaccine are a delayed hypersensitivity reaction. These reactions may occur sooner after the second dose, but they are self-limited and not associated with serious vaccine adverse effects. In contrast to immediate hypersensitivity reactions (eg, anaphylaxis, urticaria), these delayed reactions (dubbed “COVID arm”) are not a contraindication to subsequent vaccination.

Published online May 12, 2021.
Review

Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data


This is a Brighton Collaboration Case Definition of the term “Vaccine Associated Enhanced Disease” to be utilized in the evaluation of adverse events following immunization. The Case Definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for SARS-CoV-2 vaccines and other emerging pathogens. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by selected Expert Reviewers prior to submission.

© 2021 The Author(s). Published by Elsevier Ltd. All rights reserved.

Please cite this article as: F.M. Munoz, J.P. Cramer, C.L. Dekker et al., Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data, Vaccine, https://doi.org/10.1016/j.vaccine.2021.01.055

Minal K. Patel a,*, Isabel Bergeri a, Joseph S. Bresee b, Benjamin J. Cowling c, Natasha S. Crowcroft a, Kamal Fahmy d, Siddhivinayak Hirve a, Gagandeep Kang e, Mark A. Katz f, Claudio F. Lanata g, Maïna L'Azou Jackson h, Sudhir Joshi i, Marc Lipsitch j, Jason M. Mwenda k, Francisco Nogareda l, Walter A. Orenstein m, Justin R. Ortiz n, Richard Pebody l, Stephanie J. Schrag b, Peter G. Smith o, Padmini Srikantiah p, Lorenzo Subissi a, Marta Valenciano q, David W. Vaughn p, Jennifer R. Verani b, Annelies Wilder-Smith a, Daniel R. Feikin a

Interim guidance
Discussion of different study designs
Priority outcomes to evaluate
Potential biases
Existing surveillance platforms
Recommendations for reporting results

Accepted 27 May 2021 https://doi.org/10.1016/j.vaccine.2021.05.099
Association of COVID-19 Vaccination With Risk of COVID-19 Infection, Hospitalization, and Death in Heart Transplant Recipients

Laura L. Peters, DNP, FNP; David S. Raymer, MD, MPH; Jay D. Pal, MD, PhD; Amrut V. Ambarekar, MD

Key Points

**Question** Do COVID-19 vaccines provide protection against severe SARS-CoV-2 infection and death in heart transplant recipients?

**Findings** In this case-control study, heart transplant recipients from a single center who were vaccinated against SARS-CoV-2 had significantly lower risk of COVID-19 infection, hospitalization, and death with no transplant-related safety concerns.

**Meaning** Even though the immunogenic response to COVID-19 vaccination is lower in patients who receive a heart transplant, the vaccine appears to be safe and is associated with a lower risk of COVID-19 infection, hospitalization, and death, suggesting it is imperative that all heart transplant recipients obtain the COVID-19 vaccine.
Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes

Inbal Goldshtein, PhD; David M. Steinberg, PhD; Jacob Kuint, MD; Gabriel Chodick, PhD; Yaakov Segal, MD; Shirley Shapiro Ben David, MD; Amir Ben-Tov, MD

Key Points

**Question**  Is prenatal exposure to maternal BNT162b2 messenger RNA COVID-19 vaccine associated with adverse outcomes at birth or in early childhood?

**Findings**  In a population-based study including 24,288 singleton live births, the risks of preterm birth and small birth weight were similar between newborns prenatally exposed and unexposed to maternal vaccination.

**Meaning**  Maternal BNT162b2 vaccination in pregnancy was not associated with detrimental outcomes to the offspring.
Evaluation of mRNA-1273 Covid-19 Vaccine in Children 6 to 11 Years of Age


CONCLUSIONS
Two 50-μg doses of the mRNA-1273 vaccine were found to be safe and effective in inducing immune responses and preventing Covid-19 in children 6 to 11 years of age; these responses were noninferior to those in young adults. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; KidCOVE ClinicalTrials.gov number, NCT04796896.)
CONCLUSIONS AND RELEVANCE Among children and adolescents, estimated VE for 2 doses of BNT162b2 against symptomatic infection was modest and decreased rapidly. Among adolescents, the estimated effectiveness increased after a booster dose.
SARS-CoV-2 Variants and Vaccines


Evaluate efficacy of existing vaccines against variants of concern

Decide whether a new antigen is warranted

Determine which new antigen should be used

Evaluate efficacy of modified vaccines against variants of concern

Evaluate efficacy of completely new vaccines against variants of concern

Promote convergence of regulatory assessments

Figure 2. A Framework for Evaluating Vaccines against Variants of Concern.

After variants of concern are designated, the efficacy of existing vaccines is evaluated with the use of in vitro data, animal models, randomized evidence, observational studies, and surveillance.
Surveillance for Adverse Events After COVID-19 mRNA Vaccination

Nicola P. Klein, MD, PhD; Ned Lewis, MPH; Kristin Goddard, MPH; Bruce Fireman, MA; Ousseyn Zerbo, PhD; Kayla E. Hanson, MPH; James G. Donahue, DVM, PhD; Elyse O. Kharbanda, MD, MPH; Allison Nalawey, PhD; Jennifer Clark Nelson, PhD; Stan Xu, PhD; W. Katherine Yih, PhD, MPH; Jason M. Glanz, PhD; Joshua T. B. Williams, MD; Simon J. Hambidge, MD, PhD; Bruno J. Lewin, MD; Tom T. Shimabukuro, MD, MPH, MBA; Frank DeStefano, MD, MPH; Eric S. Weintraub, MPH

**MAIN OUTCOMES AND MEASURES** Incidence of serious outcomes, including acute myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, and thrombosis with thrombocytopenia syndrome. Incidence of events that occurred among vaccine recipients 1 to 21 days after either dose 1 or 2 of a messenger RNA (mRNA) vaccine was compared with that of vaccinated concurrent comparators who, on the same calendar day, had received their most recent dose 22 to 42 days earlier. Rate ratios (RRs) were estimated by Poisson regression, adjusted for age, sex, race and ethnicity, health plan, and calendar day. For a signal, a 1-sided \( P < 0.048 \) was required to keep type I error below 0.05 during 2 years of weekly analyses. For 4 additional outcomes, including anaphylaxis, only descriptive analyses were conducted.

**Meaning** This analysis found no significant associations between vaccination with mRNA COVID-19 vaccines and selected serious health outcomes 1 to 21 days after vaccination, although CIs were wide for some rate ratio estimates and additional follow-up is ongoing.
Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic

Stanley Xu a,*, Vennis Hong a, Lina S. Sy a, Sungching C. Glenn a, Denison S. Ryan a, Kerresa L. Morrissette a, Jennifer C. Nelson b, Simon J. Hambidge c, Bradley Crane d, Ousseny Zerbo e, Malini B. DeSilva f, Jason M. Glanz g, James G. Donahue h, Elizabeth Liles d, Jonathan Duffy i, Lei Qian a

Methods: We assembled a cohort of members from 8 Vaccine Safety Datalink sites from January 1, 2017 through December 31, 2020. Using ICD-10 diagnosis codes or laboratory criteria, we identified 21 incident outcomes in traditional in-person settings and all settings. We defined 4 periods in 2020: January-February (pre-pandemic), April-June (early pandemic), July-September (middle pandemic), and October-December (late pandemic). We defined four corresponding periods in each year during 2017–2019. We calculated incidence rates, conducted difference in difference (DiD) analyses, and reported ratios of incidence rate ratios (RRR) to examine changes in rates from pre-pandemic to early, middle, and late pandemic in 2020, after adjusting for changes across similar periods in 2017–2019.

Conclusion: Rates of some clinical outcomes during the pandemic changed and should not be used as historical background rates in vaccine safety studies. Inclusion of telehealth visits should be considered for vaccine studies involving Bell’s palsy, ITP, and narcolepsy/cataplexy.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, https://doi.org/10.1016/j.vaccine.2022.04.037
Incidence rates of acute myocardial infarction per 100,000 person-years over time

Fig. 1. Incidence rates of acute myocardial infarction per 100,000 person-years over time.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, https://doi.org/10.1016/j.vaccine.2022.04.037
Fig. 2. Incidence rates of anaphylaxis per 100,000 person-years over time.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, https://doi.org/10.1016/j.vaccine.2022.04.037
Fig. 3. Incidence rates of Bell’s palsy per 100,000 person-years over time.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, https://doi.org/10.1016/j.vaccine.2022.04.037
Fig. 4. Incidence rates of Guillain-Barré syndrome per 100,000 person-years over time.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, https://doi.org/10.1016/j.vaccine.2022.04.037
**Fig. 5.** Incidence rates of immune thrombocytopenia per 100,000 person-years over time.

Please cite this article as: S. Xu, V. Hong, L.S. Sy et al., Changes in incidence rates of outcomes of interest in vaccine safety studies during the COVID-19 pandemic, Vaccine, [https://doi.org/10.1016/j.vaccine.2022.04.037](https://doi.org/10.1016/j.vaccine.2022.04.037)
COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Hildale Bldg., 4th Floor
Silver Spring, MD 20993-0082
Phone: 855-543-3764 or 301-734-5400; Fax: 301-443-6553; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0082
Phone: 800-355-4709 or 240-402-8910; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2021
This document supersedes the guidance of the same title issued on May 11, 2020.
Clinical/Medical
COVID-19: Master Protocols
Evaluating Drugs and Biological Products for Treatment or Prevention
Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8019; Email: comdev@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information-guidances-drugs

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8019; Email: biocomdev@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

May 2021
Clinical/Medical
Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers

Guidance for Industry

April 2021

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
COVID-19: Developing Drugs and Biological Products for Treatment or Prevention
Guidance for Industry

This guidance describes FDA’s current recommendations regarding phase 2 and phase 3 trials for drugs under development to treat or prevent COVID-19. These recommendations focus on the population, trial design, efficacy endpoints, safety considerations, and statistical considerations for such clinical trials. The guidance addresses considerations for the treatment or prevention of acute COVID-19. It does not address drug development programs targeting the treatment of persistent or late symptoms after recovery from acute illness.

This guidance does not provide general recommendations on early drug development in COVID-19, such as use of animal models. Drugs should have undergone sufficient development before their evaluation in phase 2 or phase 3. For some biological products (e.g., cellular and gene therapies and blood products) there may be additional considerations, and FDA encourages sponsors to reach out to the applicable review division as appropriate.
Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on January 27, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)
Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).
Repurposed Drugs

• Many of the proposed drugs for COVID 19 were previously approved for other indications or under investigation for another indication
• Nonclinical and clinical safety data was already available to aid in the risk/benefit determination

• Remdesivir is an example of an investigational product repurposed for COVID 19
Coronavirus Treatment Acceleration Program (CTAP)

What is CTAP?

FDA has created a special emergency program for possible coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP). The program uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful. We continue to support clinical trials that are testing new treatments for COVID so that we gain valuable knowledge about their safety and effectiveness.
Drug-induced phospholipidosis confounds drug repurposing for SARS-CoV-2

Tia A. Tummino¹,²,³,⁴†, Veronica V. Rezeli⁵†, Benoit Fischer⁶†, Audrey Fischer⁶†, Matthew J. O’Meara⁷, Blandine Monel⁸, Thomas Vallet⁹, Kris M. White⁸,¹⁰, Ziyang Zhang³,⁴,¹¹,¹², Assaf Alon¹³, Heiko Schadt⁶, Henry R. O’Donnell¹, Jiankun Lyu¹,³,⁴, Romel Rosales⁹,¹⁰, Briana L. McGovern⁹,¹⁰, Raveen Rathnasinghe⁹,¹⁰,¹⁴, Sonia Jangra⁹,¹⁰, Michael Schotsaert⁹,¹⁰, Jean-René Galarneau¹⁵, Nevan J. Krogan³,⁴,¹¹,¹⁶, Laszlo Urban¹⁵, Kevan M. Shokat³,⁴,¹¹,¹², Andrew C. Kruse¹³, Adolfo García-Sastre⁶,¹⁰,¹⁷,¹⁸, Olivier Schwartz⁸, Francesca Moretti⁶*, Marco Vignuzzi⁸*, Francois Pognan⁶*, Brian K. Shoichet¹,³,⁴*:

Repurposing drugs as treatments for COVID-19 has drawn much attention. Beginning with sigma receptor ligands, and expanding to other drugs from screening in the field, we became concerned that phospholipidosis was a shared mechanism underlying the antiviral activity of many repurposed drugs. For all of the 23 cationic amphiphilic drugs tested, including hydroxychloroquine, azithromycin, amiodarone, and four others already in clinical trials, phospholipidosis was monotonically correlated with antiviral efficacy. Conversely, drugs active against the same targets that did not induce phospholipidosis were not antiviral. Phospholipidosis depends on the physicochemical properties of drugs, and does not reflect specific target-based activities, rather it may be considered a toxic confound in early drug discovery. Early detection of phospholipidosis could eliminate these artifacts, enabling a focus on molecules with therapeutic potential.
Remdesivir

- Pre-IND open in Feb 2015 for treatment of Ebola virus disease
  - A nucleoside inhibitor for the Ebola Virus
  - A complete Nonclinical package

- IND was received July 2015 for Ebola
  - Allowed to proceed August 2015
  - Based on early results of the Ebola Trial, it was decided that it will no longer be used for first line Ebola treatment
  - However, it was the Agency’s first consideration for Covid because of the MOA
Remdesivir for CC

• Generic MOA
  ◦ Should work for all RNA viruses
  ◦ Data demonstrating activity for SARS and MERS

• Status of Nonclinical Program
  ◦ All toxicology studies to support approval were submitted and reviewed by 2019

• No additional data were necessary to support IND for COVID

• IND was submitted for COVID in February, 2020
Remdesivir Receives Fast Track Designation

- Expedited Development/Review
  - More frequent interactions with the review team and sponsor
- EUA Determination
  - March 27, 2020: HHS Secretary declaration
  - Scientific evidence that benefits outweigh risks
- Conditions of Authorization
  - Fact Sheet for Health Care Providers
  - Information for any Recipients
  - Monitoring/Reporting Adverse Events
- NDA Submission (Rolling Review), April 2020
  - Consider reviewing portions of marketing application before the sponsor submits the complete application (CMC/Tox) (Virology/Clinical)

NDA for RDV approved in 10 weeks, May 1, 2020
Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19

Brian T. Garibaldi, MD, MEHP; Kunbo Wang, MS; Matthew L. Robinson, MD; Scott L. Zeger, PhD; Karen Bandeen-Roche, PhD; Mei-Cheng Wang, PhD; G. Caleb Alexander, MD; Amita Gupta, MD; Robert Bollinger, MD, MPH; Yanxun Xu, PhD

CONCLUSIONS AND RELEVANCE In this comparative effectiveness research study of adults hospitalized with COVID-19, receipt of remdesivir was associated with faster clinical improvement in a cohort of predominantly non-White patients. Remdesivir plus corticosteroid administration did not reduce the time to death compared with remdesivir administered alone.

Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses

WHO Solidarity Trial Consortium*

Summary
Background The Solidarity trial among COVID-19 inpatients has previously reported interim mortality analyses for four repurposed antiviral drugs. Lopinavir, hydroxychloroquine, and interferon (IFN)-β1a were discontinued for futility but randomisation to remdesivir continued. Here, we report the final results of Solidarity and meta-analyses of mortality in all relevant trials to date.

Interpretation Remdesivir has no significant effect on patients with COVID-19 who are already being ventilated. Among other hospitalised patients, it has a small effect against death or progression to ventilation (or both).
FDA Approves Remdesivir for Treatment of COVID-19 in Young Children

On April 25, 2022, the U.S. Food and Drug Administration expanded the approval of the COVID-19 treatment Veklury (remdesivir) to include pediatric patients 28 days of age and older weighing at least 3 kilograms (about 7 pounds) with positive results of direct SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

The only approved dosage form of Veklury for pediatric patients weighing 3 kg to less than 40 kg is Veklury for injection (supplied as 100 mg lyophilized powder in vial). The recommended dosage of Veklury is:

- **Adults and pediatric patients weighing at least 40 kg**: a single loading dose of Veklury 200 mg on Day 1 followed by once-daily maintenance doses of Veklury 100 mg from Day 2 via intravenous infusion.

- **Pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg**: a single loading dose of Veklury 5 mg/kg on Day 1 followed by once-daily maintenance doses of Veklury 2.5 mg/kg from Day 2 via intravenous infusion.
Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities

The I-TECH Randomized Clinical Trial

Steven Chee Loon Lim, MRCP; Chee Peng Hor, MSc; Kim Heng Tay, MRCP; Anilawati Mat Jelani, MMed; Wen Hao Tan, MMed; Hong Bee Ker, MRCP; Ting Soo Chow, MRCP; Masliza Zaid, MMed; Wee Kooi Cheah, MRCP; Han Hua Lim, MRCP; Khairil Erwan Khalid, MRCP; Joo Thye Cheng, MRCP; Hazfazila Mohd Unit, MRCP; Noralfazita An, MMed; Azraai Bahari Nasruddin, MRCP; Lee Lee Low, MRCP; Song Weng Ryan Khoo, MRCP; Jia Hui Loh, MRCP; Nor Zaila Zaidan, MMed; Suhalia Ab Wahab, MMed; Li Heng Song, MD; Hui Moon Koh, MClinPharm; Teck Long King, BPharm; Nai Ming Lai, MRCPCH; Suresh Kumar Chidambaram, MRCP; Kalaiarasu M. Peariasamy, MSc; for the I-TECH Study Group

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. The study findings do not support the use of ivermectin for patients with COVID 19
Oral Antiviral Medications for COVID-19

Two new oral antiviral medications are available for treatment of COVID-19.

**Oral antiviral medications for COVID-19: Ritonavir-boosted nirmatrelvir and molnupiravir**

*Authorized for use within 5 days of COVID-19 symptom onset in nonhospitalized patients who test positive for SARS-CoV-2 and have a high-risk underlying medical condition*

**Medication effectiveness**
- Prevents SARS-CoV-2 from multiplying
- The need for hospitalization is decreased
- Recovery from symptoms usually takes several days to 2 weeks
- Nirmatrelvir-ritonavir has been shown to be more effective than molnupiravir

**Other important facts**
- Potential side effects include altered taste, nausea, diarrhea, and dizziness
- Nirmatrelvir-ritonavir cannot be given to those with severe kidney or liver disease and medication lists need careful review for important drug interactions
- Molnupiravir should not be given to those who are pregnant, attempting to become pregnant, or aged <18 years
Assessment of 135794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States

L. Charles Bailey, MD, PhD; Hanieh Razzaghi, MPH; Evanette K. Burrows, MPH; H. Timothy Bunnell, PhD; Peter E. F. Camacho, MS; Dimitri A. Christakis, MD, MPH; Daniel Eckrich, MLIS; Melody Kitzmiller, BS; Simon M. Lin, MD, MBA; Brianna C. Magnusen, MD; Jason Newland, MD; Nathan M. Pajor, MD, MS; Daksha Ranade, MPH, MBA; Suchitra Rao, MD, MScS; Olamiji Sofela, MBChB, MMCi; Janet Zahner, BS; Cortney Bruno, MSW; Christopher B. Forrest, MD, PhD

CONCLUSIONS AND RELEVANCE In this large cohort study of US pediatric patients, SARS-CoV-2 infection rates were low, and clinical manifestations were typically mild. Black, Hispanic, and Asian race/ethnicity; adolescence and young adulthood; and nonrespiratory chronic medical conditions were associated with identified infection. Kawasaki disease diagnosis is not an effective proxy for multisystem inflammatory syndrome of childhood.

Published online November 23, 2020.
Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19

Leora R. Feldstein, PhD; Mark W. Tenforde, MD; Kevin G. Friedman, MD; Margaret Newhams, MPH; Erica Billig Rose, PhD; Heda Dapul, MD; Vijaya L. Soma, MD; Aline B. Maddux, MD; Peter M. Mourani, MD; Cindy Bowens, MD; Mia Maamari, MD; Mark W. Hall, MD; Becky J. Riggs, MD; John S. Giuliano Jr, MD; Adalok R. Singh, MD; Simon Li, MD; Michele Kong, MD; Jennifer E. Schuster, MD; Gwenn E. McLaughlin, MD; Stephanie P. Schwartz, MD; Tracee C. Welker, MD; Laura L. Loftis, MD; Charlotte V. Hobbs, MD; Natasha B. Halasa, MD; Sule Doymaz, MD; Christopher J. Babbitt, MD; Janet R. Hume, MD; Shira J. Gertz, MD; Katherine Iby, MD; Katharine N. Ciuferri, MD; Natalie Z. Cvijanovich, MD; Tamara T. Bradford, MD; Lincoln S. Smith, MD; Sabrina M. Heidemann, MD; Sheemon P. Zackai, MD; Kari Wellnitz, MD; Ryan A. Norziger, MD; Steven M. Horwitz, MD; Ryan W. Carroll, MD; Courtney M. Rowan, MD; Kesko M. Tarquinio, MD; Elizabeth H. Hickey, MD; Julie C. Fitzgerald, MD; Bria M. Coates, MD; Ashley M. Jackson, MPH; Cameron C. Young; Mary Beth F. Son, MD; Manish M. Patel, MD; Jane W. Newburger, MD; Adrienne G. Randolph, MD; for the Overcoming COVID-19 Investigators

Key Points

**Question** How do the characteristics and outcomes of children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compare with severe coronavirus disease 2019 (COVID-19)?

**Findings** In this case series that included 539 patients with MIS-C and 577 patients with severe COVID-19, patients with MIS-C were more likely than those with severe COVID-19 to be 6 to 12 years old, be non-Hispanic Black, and have severe cardiovascular or mucocutaneous involvement and more extreme inflammation.

**Meaning** The study findings suggest patterns of clinical presentation and organ involvement that distinguish between patients with MIS-C and severe acute COVID-19.
Multisystem Inflammatory Syndrome in Adults: A Rare Sequela of SARS-CoV-2 Infection

Faran Ahmad, Arslan Ahmed, Sanu S. Rajendraprasad, Austin Loranger, Sonia Gupta, Manasa Velagapudi, Renuga Vivekanandan, Joseph A. Nahas, Robert Plambeck, Douglas Moore

PII: S1201-9712(21)00452-5
DOI: https://doi.org/10.1016/j.ijid.2021.05.050
Reference: IJID 5434
To appear in: International Journal of Infectious Diseases

Received Date: 15 April 2021
Revised Date: 14 May 2021
Accepted Date: 21 May 2021

For Immediate Release:
June 24, 2021

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) (https://media/150319/download) for the drug Actemra (tocilizumab) for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Actemra is not authorized for use in outpatients with COVID-19.
Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H₂L₂ polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.
FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR ACTEMRA® (tocilizumab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use ACTEMRA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous use
Original EUA Authorized Date: 06/2021

Maximum dosage in COVID-19 patients is 800 mg per infusion.

------------------------WARNINGS AND PRECAUTIONS------------------------
- Serious Infections – do not administer ACTEMRA during any other concurrent active infection (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity – ACTEMRA treatment is not recommended in patients with elevated ALT or AST above 10 times the upper limit of the reference range. (5.3)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, and liver function tests. (5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – avoid use with ACTEMRA. (5.8)
Improved survival among hospitalized patients with COVID-19 treated with remdesivir and dexamethasone. A nationwide population-based cohort study.

Thomas Benfield, MD\textsuperscript{1,2}, Jacob Bodilsen, MD\textsuperscript{3}, Christian Brieghel, MD\textsuperscript{4}, Zitta Barrella Harboe, MD\textsuperscript{2,5}, Marie Helleberg, MD\textsuperscript{6}, Claire Holm, MD\textsuperscript{7}, Simone Bastrup Israelsen, MD\textsuperscript{1}, Janne Jensen, MD\textsuperscript{8}, Tomas Østergaard Jensen, MD\textsuperscript{6}, Isik Somuncu Johansen, MD\textsuperscript{9}, Stine Johnsen, MD\textsuperscript{7}, Birgitte Lindegaard Madsen, MD\textsuperscript{2,6}, Jens Lundgren, MD\textsuperscript{2,6,10}, Christian Niels Meyer, MD\textsuperscript{11}, Rajesh Mohey, MD\textsuperscript{12}, Lars Møller Pedersen, MD\textsuperscript{7}, Henrik Nielsen, MD\textsuperscript{3}, Stig Lønberg Nielsen, MD\textsuperscript{9}, Niels Obel, MD\textsuperscript{2,6}, Lars Haukali Omland, MD\textsuperscript{6}, Daria Podlekareva, MD\textsuperscript{7}, Birgitte Klindt Poulsen, MD\textsuperscript{13}, Pernille Ravn, MD\textsuperscript{4}, Haakon Sandholdt, MSc\textsuperscript{1}, Jonathan Starling, BSc\textsuperscript{6}, Merete Storgaard, MD\textsuperscript{14}, Christian Søborg, MD\textsuperscript{4}, Ole Schmeltz Søgaard, MD\textsuperscript{14}, Torben Tranborg, MD\textsuperscript{15}, Lothar Wiese, MD\textsuperscript{11}, Hanne Rolighed Christensen, MD\textsuperscript{16}

Conclusions and relevance

Treatment of moderate to severe COVID-19 during June through December that included remdesivir and dexamethasone was associated with reduced 30-day mortality and need of MV compared to treatment in February through May.

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
Investigational COVID-19 Convalescent Plasma

Guidance for Industry


This document supersedes the guidance of the same title issued on January 15, 2021.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2021
CONCLUSIONS

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)
Broad neutralization of SARS-related viruses by human monoclonal antibodies

Anna Z. Wec¹, Daniel Wrapp², Andrew S. Herbert³, Daniel P. Maurer¹, Denise Hashwanter⁴, Mrunal Sakharkar¹, Rohit K. Jangra⁴, M. Eugenia Dieterle⁴, Asparouh Lilov¹, Deli Huang⁵, Longping V. Tse⁶, Nicole V. Johnson², Ching-Lin Hsieh², Nianshuang Wang², Juergen H. Nett¹, Elizabeth Champney¹, Irina Burnina¹, Michael Brown¹, Shu Lin¹, Melanie Sinclair¹, Carl Johnson¹, Sarat Pudi¹, Robert Bortz III⁴, Ariel S. Wirchnianski⁴, Ethan Laukermilch⁴, Catalina Florez⁴, J. Maximilian Fels⁴, Cecilia M. O'Brien³, Barney S. Graham⁷, David Nemazee⁵, Dennis R. Burton⁵,⁸,⁹,¹⁰, Ralph S. Baric⁶,¹¹, James E. Voss⁵, Kartik Chandran⁴, John M. Dye³, Jason S. McLellan², Laura M. Walker¹

Broadly protective vaccines against known and pre-emergent human coronaviruses (HCoVs) are urgently needed. To gain a deeper understanding of cross-neutralizing antibody responses, we mined the memory B cell repertoire of a convalescent SARS donor and identified 200 SARS-CoV-2 binding antibodies that target multiple conserved sites on the spike (S) protein. A large proportion of the non-neutralizing antibodies display high levels of somatic hypermutation and cross-react with circulating HCoVs, suggesting recall of pre-existing memory B cells (MBCs) elicited by prior HCoV infections. Several antibodies potently cross-neutralize SARS-CoV, SARS-CoV-2, and the bat SARS-like virus WIV1 by blocking receptor attachment and inducing S1 shedding. These antibodies represent promising candidates for therapeutic intervention and reveal a target for the rational design of pan-sarbecovirus vaccines.
Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies

Alina Baum, Benjamin O. Fulton, Elzbieta Wloga, Richard Copin, Kristen E. Pascal, Vincenzo Russo, Stephanie Giordano, Kathryn Lanza, Nicole Negron, Min Ni, Yi Wei, Gurinder S. Atwal, Andrew J. Murphy, Neil Stahl, George D. Yancopoulos, Christos A. Kyratsous*

Regeneron Pharmaceuticals Inc., Tarrytown, NY 10591, USA.
*Corresponding author. Email: christos.kyratsous@regeneron.com

Antibodies targeting the spike protein of SARS-CoV-2 present a promising approach to combat the COVID19 pandemic; however, concerns remain that mutations can yield antibody resistance. We investigate the development of resistance against four antibodies to the spike protein that potently neutralize SARS-CoV-2, individually as well as when combined into cocktails. These antibodies remain effective against spike variants that have arisen in the human population. However, novel spike mutants rapidly appeared following in vitro passaging in the presence of individual antibodies, resulting in loss of neutralization; such escape also occurred with combinations of antibodies binding diverse but overlapping regions of the spike protein. Importantly, escape mutants were not generated following treatment with a non-competing antibody cocktail.
Emergency Use Authorization (EUA) for casirivimab and imdevimab

Center for Drug Evaluation and Research (CDER) Review 12/14/2020

XII. Nonclinical Data to Support Safety

- Casirivimab and imdevimab were evaluated either alone or administered together in a GLP 4-week repeat-dose toxicology study in cynomolgus monkeys with an 8-week recovery using both intravenous and subcutaneous dosing.
  - No adverse, drug-related findings were observed in this study up to the highest doses tested (150 mg/kg/mAb) by either the intravenous or subcutaneous routes. The safety factor at the NOAEL of 150 mg/kg/mAb, based on body surface area, is 7.5 relative to the proposed human dose of 1200 mg/mAb in a 60-kg adult.
  - Minor, non-adverse liver toxicity (~2- to 3-fold increases in AST, ALT and LDH) were observed at the high dose on Day 2 and 7, but appeared to recover by Day 27. No histopathology correlates were observed.
- GLP tissue cross-reactivity studies were also conducted in both normal adult and select fetal human and cynomolgus monkey tissues. No binding of clinical concern was observed with either casirivimab or imdevimab in either species in these studies.
FDA NEWS RELEASE


For Immediate Release:
February 09, 2021

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) (https://www.fda.gov/media/145801/download) for bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.
Frequently Asked Questions on the Revocation of the Emergency Use Authorization for Bamlanivimab Administered Alone (EUA 90)

Q. Why was the Emergency Use Authorization (EUA) for bamlanivimab administered alone (EUA 90) revoked?

A. FDA is required to regularly review the circumstances and appropriateness of an Emergency Use Authorization (EUA), including review of emerging scientific data associated with the emergency use of an authorized product. Since the initial authorization of bamlanivimab administered alone for emergency use on November 9, 2020, there has been a sustained increase in SARS-CoV-2 viral variants across the U.S. that are resistant to bamlanivimab alone. Given the frequency of these particular viral variants, and since current testing technologies are not available to ascertain whether a particular patient who has tested positive for coronavirus disease 2019 (COVID-19) is infected with a viral variant prior to initiation of treatment, there is an increased risk of treatment failure when bamlanivimab is administered alone. As such, based on the totality of scientific evidence available, the Agency has concluded that the known and potential benefits of bamlanivimab administered alone no longer outweigh the known and potential risks for the product. Therefore, the Agency has determined that the criteria for issuance of an EUA are no longer met and has revoked EUA 90 for bamlanivimab administered alone for the treatment of COVID-19.
FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

This EUA is for the use of the unapproved product sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see Limitations of Authorized Use].
Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab.
Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC\textsubscript{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, lung weight, total viral RNA in the lungs, or infectious virus levels based on TCID\textsubscript{50} measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.
Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency

Guidance for Industry

February 2021
Sponsors of monoclonal antibody products targeting SARS-CoV-2 should consider the following pharmacology toxicology recommendations:

- The Agency intends to be flexible regarding selected nonclinical safety data submission expectations (e.g., timing of data submission to the IND) for monoclonal antibody products targeting SARS-CoV-2 to support clinical trial initiation. The degree of flexibility warranted will be influenced by the benefit-risk assessment for the intended population (e.g., hospitalized, nonhospitalized, healthy trial subjects) and the potential coverage of important emerging variants. Thus, FDA strongly recommends that sponsors discuss the nonclinical requirements to support product administration in a specific clinical trial with the Agency through the pre-IND consultation process.\textsuperscript{11}
A tissue cross reactivity (TCR) study using a panel of human tissues. When a monoclonal antibody binds to human tissues in the TCR study, FDA recommends evaluating monoclonal antibody binding to select tissues from nonclinical species to assist in species selection for repeat-dose toxicology testing. When binding of potential clinical concern is observed (e.g., cell membrane binding), FDA recommends discussing these data with the Agency because additional studies may be needed to help inform the potential clinical relevance of the findings.
A short duration (i.e., 3 weeks of treatment) repeat-dose toxicology study in a single species, using the clinical formulation and route of administration(s) intended for clinical administration, that includes all standard toxicity endpoints including toxicokinetic analysis. FDA also recommends discussing specific study design considerations with the Agency.

- Toxicology studies with specific monoclonal antibody combinations are not needed for monoclonal antibody products targeting SARS-CoV-2 proteins, so monoclonal antibody products can be evaluated separately in toxicology studies. If a sponsor evaluates monoclonal antibody products in combination, FDA recommends using the same ratio intended for clinical administration.

- To support administration of monoclonal antibody products during pregnancy, FDA recommends conducting a TCR study using relevant human tissues or studies using alternative protein interaction technologies, with appropriate justification. If no specific concerns are identified in the repeat-dose toxicology and TCR studies, developmental and reproductive toxicology studies are not needed.
Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Summary

Background Casirivimab and imdevimab are non-competing monoclonal antibodies that bind to two different sites on the receptor binding domain of the SARS-CoV-2 spike glycoprotein, blocking viral entry into host cells. We aimed to evaluate the efficacy and safety of casirivimab and imdevimab administered in combination in patients admitted to hospital with COVID-19.

Interpretation In patients admitted to hospital with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality in patients who were seronegative (and therefore had not mounted their own humoral immune response) at baseline but not in those who were seropositive at baseline.
Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase


The New England Journal of Medicine

Downloaded from nejm.org on September 29, 2021. For personal use only. No other uses without permission.
Copyright © 2021 Massachusetts Medical Society. All rights reserved.
A  Covid-19 Events, Per-Protocol Analysis

Vaccine Efficacy (95% CI)  
93.2 (91.0–94.8)  

Incidence Rate (95% CI)  
9.6 (7.2–12.5)  
136.6 (127.0–146.8)

Cumulative Incidence (%)  

Days since Randomization

No. at Risk  
Placebo  
mRNA-1273  

| No. at Risk | 14,164 | 14,164 | 14,134 | 13,030 | 13,733 | 12,970 | 11,199 | 7783 | 3323 | 953 | 336 | 64 | 5 | 0  
mRNA-1273  | 14,287 | 14,287 | 14,281 | 14,246 | 14,096 | 13,584 | 12,196 | 9031 | 4252 | 1375 | 473 | 49 | 2 | 0  

Placebo
COVID-19 Vaccination—Becoming Part of the New Normal

Nonetheless, it is time to accept that the presence of SARS-CoV-2, the virus that causes COVID-19, is the new normal. It will likely circulate globally for the foreseeable future, taking its place alongside other common respiratory viruses such as influenza.
Conclusions

• The most effective public health tool to control the Covid pandemic is vaccination

• Re-purposing compounds that were in development for other indications a promising avenue

• Treatment of symptoms will continue to be important

• Efficacy of convalescent plasma remains undemonstrated

• Anti-viral monoclonal antibodies have great promise