Arthur Kim, Esq. (SBN 212700)
ARTHUR KIM LAW FIRM
9440 Santa Monica Blvd, Ste 301
Beverly Hills, CA 90210
Tel: (310) 246-0316
Fax: (310) 246-0328
akim@arthurkimlaw.com

777 E. Tahquitz Canyon Way, Ste 200
Palm Springs, CA 92262
Tel: (760) 983-7242
Fax: (760) 983-7243

Attorney for Plaintiff GEORGIA RINGLER

SUPERIOR COURT FOR THE STATE OF CALIFORNIA

IN AND FOR COUNTY OF SAN DIEGO

GEORGIA RINGLER, an individual, Plaintiff, v. THE SCRIPPS RESEARCH INSTITUTE, and DOES 1-100, inclusive, Defendants.	Case No. 37-2022-00024191-CU-WT-CTL **DECLARATION OF ROBERT W. MALONE, M.D., IN SUPPORT OF PLAINTIFF GEORGIA RINGLER'S OPPOSITION TO DEFENDANT THE SCRIPPS RESEARCH INSTITUTE'S MOTION FOR SUMMARY JUDGMENT, OR IN THE ALTERNATIVE SUMMARY ADJUDICATION** Date: October 27, 2023 Time: 9:30 a.m. Dept: C-66 Filed: June 21, 2022 Trial Date: March 15, 2024

I, Robert W. Malone, M.D., declare as follows:

1. I have personal knowledge of the matters alleged herein and could and would competently testify to these matters if requested to do so at deposition, trial or court hearing.

2. I have been retained by Plaintiff Georgia Ringler's counsel, Arthur Kim Law Firm, to provide expert opinions in this matter.

3. Attached hereto as Exhibit A is a true and correct copy of my curriculum vitae, which provides a history of my education and a history of my professional experience, activities and accomplishments. The information contained in my curriculum vitae is true and accurate.

4. I was asked to answer three questions by Plaintiff's counsel, Arthur Kim. The questions were posed to me in written form. Attached as Exhibit B is a true and correct copy of the instruction sheet that Mr. Kim forwarded to me, which I reviewed.

5. Mr. Kim also forwarded me the following documents for me to review as needed: Transcript of the deposition of Karen Hagenmiller; Documents bates numbered P1-P187 and TSRI00000001 to TSRI00000541; Plaintiff Georgia Ringler's Complaint for Damages; Defendant The Scripps Research Institute's Memorandum of Points and Authorities in Support of Its Motion for Summary Judgment or, Alternatively, Summary Adjudication of Issues; Declaration of Virginia Chambers in Support of Defendant The Scripps Research Institute's Motion for Summary Judgment, or Alternatively, Summary Judgment; Declaration of Karen Hagenmiller in Support of Defendant The Scripps Research Institute's Motion for Summary Judgment, or Alternatively, Summary Judgment; Declaration of Anna-Marie Rooney in Support of Defendant The Scripps Research Institute's Motion for Summary Judgment, or Alternatively, Summary Judgment; Declaration of Daniel C. Gunning in Support of Defendant The Scripps Research Institute's Motion for Summary Judgment, or Alternatively, Summary Judgment; and Exhibits 1-22 in Support of Defendant The Scripps Research Institute's Motion for Summary Judgment, or Alternatively, Summary Judgment. I reviewed these records as needed to form my expert opinions.

6. I am qualified to give an expert opinion on the matters requested by Mr. Kim because of my educational and professional background, which is detailed in my curriculum vitae (Exhibit A). This includes my professional experience as the original inventor of mRNA and DNA vaccination technologies (with nine issued patents) as well as in-vitro and in-vivo RNA transfection and multiple non-viral DNA and RNA/mRNA delivery technologies (mRNA as a drug).

7. This includes my long career as a scientist and physician specializing in clinical research, medical affairs, regulatory affairs, project management, proposal management, vaccines and biodefense. I have written, developed, reviewed and managed vaccine, bio-threat and biologics

clinical trials and clinical development strategies. I have been involved in developing, designing, and providing oversight of approximately forty phase 1 clinical trials and twenty phase 2 clinical trials, as well as five phase 3 clinical trials. I have served as medical director/medical monitor on both phase 1, phase 2 and phase 3 clinical trials, including those run at well-known vaccine-focused Clinical Contract Research Organizations. I have served as principal investigator on some of these. Examples of my infectious disease pathogen advanced (clinical phase) development oversight experience include HIV, Influenza (seasonal and pandemic), Plague, Anthrax, VEE/EEE/WEE, Tularemia, Tuberculosis, Ebola, Zika, Ricin toxin, Botulinum toxin, and Engineered pathogens. In many cases, my experience has included vaccine product development, manufacturing, regulatory compliance, and testing (manufacturing release and clinical) aspects. In most cases, my oversight responsibilities have included clinical trial design, regulatory and ethical compliance, and laboratory assay strategy, design, testing and performance.

8. I have a history of assembling and managing expert teams that focus on solving complicated biodefense challenges to meet US Government requirements. I was instrumental in enabling the PHAC/rVSV ZEBOV ("Merck Ebola") vaccine to move forward quickly towards BLA and (now recently granted) licensure.

9. I led a large team from January 10, 2020 to March 2022, focused on clinical research design, drug development, computer modeling and mechanisms of action of repurposed drugs for COVID-19 treatment. This work has included multiple manuscripts summarizing most recent findings relating to famotidine and overall insights into the mechanism of COVID-19 disease.

10. I was scientifically trained at UC Davis, UC San Diego, and at the Salk Institute Molecular Biology and Virology laboratories. I received my medical training at Northwestern University (M.D.) and Harvard University (Clinical Research Post Graduate Fellowship) medical schools, and in Pathology at UC Davis. I am a Maryland Board of Health licensed Physician and Surgeon #DOO55466.

11. I have extensive research and development experience (bench to bedside) in the areas of pre-clinical discovery research, clinical trials, vaccines, gene therapy, bio-defense, repurposing drugs for infectious diseases, high throughput screening and immunology. I have over twenty years of

management and leadership experience in academia, pharmaceutical and biotechnology industries, as well as in governmental and non-governmental organizations. I often serve as study section chairperson for NIAID[1] contract study sections relating to biodefense medical product development. I was a topic editor for the journal *Frontiers in Pharmacology*, in the area of "Treating COVID-19 With Currently Available Drugs."

12. I have approximately 100 peer-reviewed publications and published abstracts and have about 14,000 citations of my peer reviewed publications and patents, as verified by Google Scholar. My google scholar ranking is "outstanding" for impact factors. I have been an invited speaker at 100+ scientific conferences, have chaired numerous conferences and have sat on or served as chairperson on numerous NIAID and DoD[2] study sections. I have testified at the US State Senate, the Texas State Senate, the Tennessee State Senate and the Louisiana State Senate. I have also spoken at the European Parliament (May, 2023), the Roman Senate in Italy (2021) and in the Mexican Senate (2023).

13. My qualification further includes my detailed experience in tracking the events and US Government communications during the SARS-CoV-2 Coronavirus outbreak during 2021, and having worked as a consultant to US DoD/DTRA[3] and serving on the NIH ACTIV[4] committee on behalf of US DoD/DTRA during the SARS-CoV-2 Coronavirus outbreak during 2021.

14. In response to Mr. Kim's request, I spent approximately 8.5 hours conducting an independent investigation and forming my expert opinions. In addition to reviewing the materials sent by Mr. Kim, I reviewed scientific articles and information released by public health entities to the public during the relevant time period. Based on my previous experience detailed above, the materials sent by Mr. Kim, and information I reviewed in the course of my investigation, I had sufficient information to render an expert opinion on the matters requested by Mr. Kim.

15. I provided Mr. Kim a written report of my opinions. Attached as Exhibit C is a true and correct copy of the written report containing my opinions. The report is a true statement of my opinions and a true statement of the facts that I relied upon to form those opinions. All the facts stated

[1] The National Institute of Allergy and Infectious Diseases (NIAID) is one of the institutes and centers that make up the National Institutes of Health (NIH), an agency of the United States Department of Health and Human Services.
[2] United States Department of Defense.
[3] Defense Threat Reduction Agency (DTRA) is an agency within the United States Department of Defense.
[4] Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) was a public-private partnership announced by the NIH.

in my report are true and correct to the best of my knowledge. The facts stated in my report are based on my personal knowledge or the facts are found in sources that I and other experts in my fields of expertise (scientist and physician specializing in clinical research, medical affairs, regulatory affairs, vaccines and biodefense) normally rely upon to form expert opinions.

16. Mr. Kim's first question asked: "**Was there an alternative to vaccination of Plaintiff – *for example, daily PCR testing by Plaintiff and daily certification by Plaintiff regarding Covid symptoms* – that would have provided equivalent health and safety to the Scripps community?**"

17. In response to Mr. Kim's first question, I provided the following opinion: "Therefore, if Plaintiff Ms. Ringler were to have been provided the opportunity to certify thrice weekly, in accordance with the NIH protocol published 15 September 2021, or even daily testing as Plaintiff had indicated willingness to perform, and by Plaintiff demonstrating evidence of the absence or presence of SARS-CoV-2-derived nucleic acids[5] or clinical COVID symptoms, coupled to compliance with appropriate quarantine procedures including working from home and/or avoidance of TSRI workplace(s) in the event of evidence of SARS-CoV-2 nucleic acid or COVID symptoms, this would have provided **clearly superior protection of other members of the TSRI community** from any infection which plaintiff Ms. Ringler might have contracted. Based on these NIH data, such testing would have provided at least 98% sensitivity in detection of an infection, in contrast to vaccination providing somewhere in the range of 66% to 37% (after three doses) to virtually no protection against SARS-CoV-2 infection."

18. As detailed in my report, this opinion is based on the following: On August 27, 2021, the CDC[6] journal Morbidity and Mortality Weekly Report (MMWR) published the results of a large study assessing "Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021" which provides an estimate of the effectiveness (through August 14, 2021) of all COVID-19 vaccines available in USA to TSRI employees.[7] The CDC study

[5] SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) is the virus that causes COVID-19 (Coronavirus disease 2019). The two main classes of nucleic acids are DNA and RNA. Nucleic acids are biopolymers, macromolecules, essential to all known forms of life. They carry information in cells and make up genetic material.

[6] The Centers for Disease Control and Prevention (CDC) is the national public health agency of the United States.

[7] Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December

also examined whether vaccine effectiveness differs for adults with increasing time since completion of all recommended vaccine doses. In the abstract summarizing this study, the **CDC noted that SARS-CoV-2 B.1.617.2 (Delta) variant predominance (the predominant SARS-CoV-2 strain circulating at the time of the plaintiff's termination) coincided with an increase in reported COVID-19 vaccine breakthrough infections.**

19. In this MMWR publication, with CDC staff as lead authors, the study reports that: *"During Delta variant–predominant weeks at study sites, 488 unvaccinated participants contributed a median of 43 days (IQR = 37–69 days; total = 24,871 days) with 19 SARS-CoV-2 infections (94.7% symptomatic); 2,352 fully vaccinated participants contributed a median of 49 days (IQR = 35–56 days; total = 119,218 days) with 24 SARS-CoV-2 infections (75.0% symptomatic). Adjusted* ***VE[8] during this Delta predominant period was 66% (95% CI = 26%–84%) compared with 91% (95% CI = 81%–96%) during the months preceding Delta predominance****."*

20. Delta was the dominant SARS-CoV-2 variant at the time plaintiff Ms. Ringler's employment with TSRI was terminated (September 15, 2021), but at that time, the Delta variant was beginning to be displaced by the Omicron variant. In a preprint originally posted on the MedRxIV server on January 01, 2022, and subsequently published in JAMA Network on September 22, 2022, it was reported that receipt of 2 doses of COVID-19 vaccines was not protective against Omicron. In that study, vaccine effectiveness against Omicron was measured at 37% (95%CI, 19-50%) ≥7 days after receiving an mRNA vaccine for the third dose.[9]

21. **Therefore, depending on whether a hypothetical TSRI employee such as the plaintiff were to be infected with either the Delta or Omicron variants of SARS-CoV-2, these data from that time period indicate the vaccine effectiveness of the mRNA vaccines for COVID**

2020–August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1167-1169.
DOI: http://dx.doi.org/10.15585/mmwr.mm7034e4external icon (a true and correct copy of this article is attached hereto as Exhibit D).

[8] Vaccine effectiveness (VE). Vaccine effectiveness is a measure of how well vaccination protects people against infection, symptomatic illness, medically attended illness, including emergency department and urgent care visits, and severe illness, including hospitalization and death.

[9] Sarah A. Buchan, Hannah Chung, Kevin A. Brown et al. Effectiveness of COVID-19 vaccines against Omicron or Delta infection. medRxiv 2021.12.30.21268565; doi: https://doi.org/10.1101/2021.12.30.21268565 (a true and correct copy of this article is attached as Exhibit E).

available at that time would be in the range of 66% (44% failure to protect) to "not effective" (complete failure to protect) for prevention of infection after two doses.

22. In contrast, if the plaintiff Ms. Ringler and TSRI were to have employed PCR or rapid antigen testing every three days in accordance with the NIH-published study entitled "Longitudinal Assessment of Diagnostic Test Performance Over the Course of Acute SARS-CoV-2 Infection", then the TSRI would have benefitted from an approximately 98% sensitivity for detecting infection in staff including Ms. Ringler.

23. Quoting from the study conclusions: "RT-qPCR tests are more effective than antigen tests at identifying infected individuals prior to or early during the infectious period and thus for minimizing forward transmission (given timely results reporting). All tests showed >98% sensitivity for identifying infected individuals if used at least every 3 days. Daily screening using antigen tests can achieve approximately 90% sensitivity for identifying infected individuals while they are viral culture positive."[10]

24. Finally, based on the information known to both CDC and the public as of July 30, 2021, the cited literature, and subsequent additional peer reviewed literature including that noted above concerning the leakiness of the available vaccines, it is highly likely that rigorous examination of TSRI employee health records will reveal multiple examples of vaccinated TSRI employees who contracted SARS-CoV-2 infection with or without COVID disease despite being fully compliant with TSRI vaccination policy, which would clearly demonstrate the failure of the TSRI proposed public health measures to achieve the objective of eliminating the risk of SARS-CoV-2 infection or COVID disease in TSRI employees and other persons associated with TSRI via a vaccination requirement.

25. As documented by the Washington Post on July 29, 2021 in the following two public disclosures relating to an internal CDC slide deck[11], it had become public knowledge that the vaccines

[10] Rebecca L Smith, Laura L Gibson, Pamela P Martinez et al. Longitudinal Assessment of Diagnostic Test Performance Over the Course of Acute SARS-CoV-2 Infection. The Journal of Infectious Diseases, Volume 224, Issue 6, 15 September 2021 (published online on June 30, 2021), Pages 976–982, https://doi.org/10.1093/infdis/jiab337 (a true and correct copy of this article is attached hereto as Exhibit F). A true and correct copy of an NIH news release on June 30, 2021, regarding this study is attached hereto as Exhibit G.

[11] *Yasmeen Abutaleb, Carolyn Y. Johnson and Joel Achenbach, "'The war has changed': Internal CDC document urges new messaging, warns delta infections likely more severe. The internal presentation shows that the agency thinks it is struggling to communicate on vaccine efficacy amid increased breakthrough infections" Washington Post- July 29, 2021 at*

available for the plaintiff Ms. Ringler to potentially use were leaky, and did not prevent infection, replication, and spread of SARS-CoV-2 virus in vaccinated persons. "Leaky" is a common technical term in vaccinology meaning that a vaccine recipient is prone to "breakthrough infections". Therefore, based on these data, knowledge and documentation were available to the general public including TSRI on or before July 29, 2021 that these available vaccines would not and could not prevent infection or spread of SARS-CoV-2 and COVID disease. Furthermore, based on this publicly disclosed CDC slide deck, even if 100% of TSRI employees were so vaccinated and all employed CDC best practices in use of particle masks, "herd immunity" or collective protection from SARS-CoV-2 infection, replication, transmission and associated COVID-19 disease could not be prevented by use of these vaccine products.

26. Mr. Kim's second question asked: "**Was this knowledge available on September 14, 2021?**"

27. In response to Mr. Kim's second question, I provided the following opinion: "As documented, this knowledge was available to the general public and TSRI on or before July 30, 2021, well before September 14, 2021."

28. I provided a further opinion in my report. According to document bates numbered P60 to P62, a fact sheet from the Charlotte Lozier Institute:

•The fetal cell line PER.C6 was used in the development or production of the Johnson & Johnson vaccine.

•The fetal cell line HEK293 was used in the testing of the Moderna vaccine.

•The fetal cell line HEK293 was used in the testing of the Pfizer vaccine.

8:58 p.m. EDT https://www.washingtonpost.com/health/2021/07/29/cdc-mask-guidance/ (a true and correct copy of this article is attached hereto as Exhibit H).

Washington Post

"Read: Internal CDC document on breakthrough infections: An internal CDC document urges officials to "acknowledge the war has changed" and improve the public's understanding of breakthrough infections." Washington Post - Updated Jul 30, 2021 at 10:15 AM (Provides copy of official CDC slide deck) https://www.washingtonpost.com/context/cdc-breakthrough-infections/94390e3a-5e45-44a5-ac40-2744e4e25f2e/ (a true and correct copy of the article and slide deck is attached hereto as Exhibit I).

These are true statements based on the cited fact sheet as well as multiple sources of information widely distributed and generally known to the public and TSRI.

29. I am available to appear at a deposition or in court to testify regarding my opinions and provide further information as needed regarding my opinions.

I declare, under penalty of perjury, under the laws of the State of California that the foregoing is true and correct. Executed this 11th day of October 2023.

Robert W. Malone, M.D.

Exhibit A

Robert W. Malone, MD, MS
Madison, VA 22727
rwmalonemd@gmail.com
(434) 979-0090

PROFESSIONAL EXPERIENCE

The original inventor of mRNA and DNA vaccination technologies (1989, with nine issued patents) as well as in-vitro and in-vivo RNA transfection and multiple non-viral DNA and RNA/mRNA delivery technologies (mRNA as a drug).

Dr. Malone is a scientist and physician, who specializes in clinical research, medical affairs, regulatory affairs, project management, proposal management (large grants and contracts), vaccines and biodefense. This includes writing, developing, reviewing and managing vaccine, bio-threat and biologics clinical trials and clinical development strategies. He has been involved in developing, designing, and providing oversight of approximately forty phase 1 clinical trials and twenty phase 2 clinical trials, as well as five phase 3 clinical trials. He has served as medical director/medical monitor on both phase 1, phase 2 and phase 3 clinical trials, including those run at well-known vaccine-focused Clinical Contract Research Organizations. He has served as principal investigator on some of these. Examples of his infectious disease pathogen advanced (clinical phase) development oversight experience include HIV, Influenza (seasonal and pandemic), Plague, Anthrax, VEE/EEE/WEE, Tularemia, Tuberculosis, Ebola, Zika, Ricin toxin, Botulinum toxin, and Engineered pathogens. In many cases, this experience has included vaccine product development, manufacturing, regulatory compliance, and testing (manufacturing release and clinical) aspects. In most cases, his oversight responsibilities have included clinical trial design, regulatory and ethical compliance, and laboratory assay strategy, design, testing and performance.

Dr. Malone has a history of assembling and managing expert teams that focus on solving complicated biodefense challenges to meet US Government requirements. He was instrumental in enabling the PHAC/rVSV ZEBOV ("Merck Ebola") vaccine to move forward quickly towards BLA and (now recently granted) licensure.

Dr. Malone led a large team from January 10, 2020 to March 2022, focused on clinical research design, drug development, computer modeling and mechanisms of action of repurposed drugs for COVID-19 treatment. This work has included multiple manuscripts summarizing most recent findings relating to famotidine and overall insights into the mechanism of COVID-19 disease.

Scientifically trained at UC Davis, UC San Diego, and at the Salk Institute Molecular Biology and Virology laboratories, Dr. Malone received his medical training at Northwestern University (MD) and Harvard University (Clinical Research Post Graduate Fellowship) medical schools, and in Pathology at UC Davis.

He has extensive research and development experience (bench to bedside) in the areas of pre-clinical discovery research, clinical trials, vaccines, gene therapy, bio-defense, repurposing drugs for infectious diseases, high throughput screening and immunology. He has over twenty years of management and leadership experience in academia, pharmaceutical and biotechnology industries, as well as in governmental and non-governmental organizations. He often serves as study section chairperson for NIAID

contract study sections relating to biodefense medical product development. He was a topic editor for the journal Frontiers in Pharmacology, in the area of "Treating COVID-19 With Currently Available Drugs."

Dr. Malone has approximately 100 peer-reviewed publications and published abstracts and has about 14,000 citations of his peer reviewed publications and patents, as verified by Google Scholar. His google scholar ranking is "outstanding" for impact factors. He has been an invited speaker at 100+ scientific conferences, has chaired numerous conferences and he has sat on or served as chairperson on numerous NIAID and DoD study sections.

Dr. Malone has testified at the US State Senate, the Texas State Senate, the Tennessee State Senate and the Louisiana State Senate.

Dr. Malone has also spoken at the European Parliament (May, 2023), the Roman Senate in Italy (2021) and in the Mexican Senate (2023). Dr. Malone informally supports congress people and the senators in various, ongoing investigations and has had a consultation with an official at the Vatican.

Dr. Malone has been featured on many TV shows and podcasts, including Joe Rogan (after which Dr Malone's episode was the #1 podcast in the world and about a 100 million listeners for this single podcast), Fox News with Tucker Carlson, the War Room with Steve Bannon, Mercola, Glen Beck, Laura Ingraham, Epoch Times, News Max, OAN, Candice Owens, The American Thinker, The High Wire with Del Bigtree, Lou Dobbs, The Dark Horse Studio and dozens more. Please search Spotify or Apple Podcasts ("Robert Malone") for listings. Dr. Malone has been featured in a number of full-length documentaries. His editorials have been published in the Washington Times, Trial Site News, The Brownstone Institute, and The American Thinker and his work has been featured on Real Clear Politics. Most recently he has presented at the Salt and Light Conference, CPAC, the Heritage Foundation, the Congressional Wife's Club, Freedom Fest, CNP, many health summits and was a keynote speaker at the John Birch Society national conference, amongst many other speaking engagements.

Dr. Malone's Substack is written almost daily and via direct email reaches 315,000 subscribers. The daily readership of his Substack averages three quarters of a million people. These articles are often picked up by aggregator news sites.

His bestselling book *Lies my Government Told Me and the Better Future Coming,* was published in 2022.

SUMMARY OF ACCOMPLISHMENTS / SKILLS

- Inventor of mRNA and DNA vaccination as well as mRNA as a drug, with nine issued patents – priority date 1989.
- Inventor of lipid mediated and naked mRNA delivery (transfection).
- Inventor of in-vivo electroporation technologies (particularly for skin delivery).
- A senior executive and scientist with a highly successful track record of leading bench and discovery research through FDA Phase I, II, and III clinical trials, protocol development and submission, and related regulatory submissions including pIND and IND.
- Significant expertise in drug development and delivery.
- Specialist in Medical Affairs and Regulatory Affairs.
- Domestically trained, Maryland Licensed Physician/Scientist.

- Experienced capturing and managing large federal contracts (including BARDA) with over 9 billion in ID/IQ awards and almost a billion USD in government contracts won and/or managed in the last decade.
- Expertise in pathology, infectious disease, pandemic clinical trials, influenza, regulatory affairs, project management, biodefense, HIV and Ebola. A verified list of capture is available upon request.
- Significant expertise with federal contracting, grants, international NGO health related research and development coupled with professional relationships at CDC, DoD, HHS (BARDA, CDC, FDA and NIAID).
- Prior and current service on many federal study sections and oversight boards involving infectious disease, vaccine, and biodefense.
- Experienced business development professional, project manager, capture/proposal manager, color team reviewer and editor for projects valued from 10M$ up to 1B$ US.
- Highly skilled in fostering a culture of innovative problem solving within project teams.
- DoD Secret Clearance authorized.
- Expert witness experience, with extensive training from some of the top attorneys/law firms in the USA.
- Rated outstanding for impact factors (with a ranking of full professor), by Google scholar.
- Graduated from the Harvard Medical School Global Clinical Scholars Research Training Program with distinction, a year-long program focused on international clinical research. Experienced in TV, media and podcaster.
- Experienced journalist and thought leader, with 750,000 daily readers of his daily news and opinion articles (rwmalonemd.substack.com).
- His published articles have almost 14,000 citations and his Google Scholar i19 Index ranks him as an “outstanding” full professor.

RW Malone MD, LLC
CEO and Principal Consultant: 2001-Present

Dr. Malone has been involved in developing, designing, and providing oversight of approximately forty phase-1 clinical trials and twenty phase-2 clinical trials, as well as five phase 3 clinical trials. He has served as medical director/medical monitor on approximately forty phase-1 clinical trials, and on twenty phase-2 clinical trials, including those run at vaccine-focused Clinical Research Organizations. He has served as principal investigator on some of these. Providing business development, proposal management, clinical trials development, expert witness, regulatory and medical affairs support for pharmaceutical, vaccines-related and biologics companies as well as related regulatory submissions including pIND and IND.
The consulting aspect of this company ended in 2021. The focus is now on independent writing projects, speaking engagements and podcasting.

Owner and writer of the "*Who is Robert Malone*" Substack: RWMaloneMD.substack.com The rwmalonemd.substack.com has a subscriber base of 308,000 and a daily total readership of 700,000.

RW Malone MD, LLC Past Projects include:

.

- Chief Medical and Regulatory Officer for the Unity Project. October 2021 to present.
- Led a large team since January 10, 2020, focused on drug development, computer modeling and mechanisms of action for COVID-19 and is now preparing a manuscript summarizing most recent findings relating to famotidine and overall insights into the mechanism of COVID-19 disease.
- Accelerated COVID-19 Therapeutic Interventions and Vaccines:
  ACTIV Therapeutics Clinical Working Group for repurposed drugs, NIH. Invited non-voting Participant. From June 2020 to Jan 2022.
- Clinical trials protocol development: Developed and wrote initial clinical trial design: A Single Center, Randomized, Double Blinded Controlled Crossover Observational Outpatient Trial of the Safety and Efficacy of Oral Famotidine for the Treatment of COVID-19 in Non-Hospitalized Symptomatic Adults.
- Proposed is a DOMANE/WRAIR joint development and performance of outpatient clinical trial designed to test new monitoring and data capture technology while using COVID19 and repurposed drugs as a live-fire example.
- Opening IND for famotidine use for treatment and prevention of COVID19 disease with associated drug master file.
- Principal Regulatory Consultant, Clinical Network Services (CNS)/Novotech, 2018-2019. Regulatory, clinical and business development support.
- Served as an expert witness with specialized training, 2017 - present.
- Ebola vaccine project for NewLink/Bioprotection Systems (rVSVdG ZEBOV Ebola vaccine project), resulting in well over 100M USD non-dilutive capital to NL/BPS. This also included working with the World Health Organization as well as initial set up of the licensing deal to Merck Vaccines of the Ebola vaccine.
- Served as Medical Director, Beardsworth, half time position on retainer, 2010 – 2013.
- Service on federal biotechnology/vaccines proposal study sections (multiple).
- Served as Editor-In-Chief of Journal of Immune Based Therapies and Vaccines 2007-2012

- Service on Safety Monitoring Committee, Phase 1 safety/immunogenicity of novel Influenza vaccine
- Consulting support for multiple vaccine-focused clinical sites in US and Latin America.
- Served as Medical Director, Vaccines with Accelovance, Inc. (2008 – 2009).
- Served as medical monitor for multiple seasonal and pandemic (H1N1) studies.
- Review and edit clinical protocols.
- Examples of multi-year contract clients include Accelovance, Alchem Laboratories, Avancer, Beardsworth, Chesapeake Perl, Corium, DOAR, ITS, ITT-Exelis, EpiVax, Jean Brown Research, Opgen, Quest Diagnostics (Focus), PaxVax, SAI, Soligenix, TASC, Univ of MA.
- Commercial intelligence work for two of the largest pharmaceutical companies in the world (sub-contractor).
- Partnering with Galloway and Associates (Darrell Galloway) 2012-2014.
- Acting as *Managing Director, Clinical Development and Government Affairs* for the Avancer Group. April 2012 – 2016.
- Proposal development (patch-based vaccine delivery, Tularemia vaccine, CDC contract for clinical trials site development, international government and NGO contract and grant solicitations) – Aeras Global TB Vaccine Foundation 2003-2005.
- Proposal development (plague vaccine- HHS), Technical diligence – VaxGen Corporation.
- Consulting services for EpiVax, 2005-2018 (member, Scientific Advisory Board), 2020.
- Consulting services for Aldevron, LLC.
  2001-2005 (operating as Gene Delivery Alliance).
- Business and proposal development in the areas of Bioinformatics and Life Sciences (including telemedicine) and research at the University of Bern, Switzerland.
- Consulting services for Molecular Histology, Inc. with the title of Medical Director.
- Collaboration with Inovio (DNA vaccines), including incorporation of company in the USA.
- Consulting services for MSD, Inc. for business/ technology development planning.

Global Health Alliance
President
Global Health Alliance manages the Global COVID Summit, that is 17,000 physicians strong and has held large seminars and conferences worldwide. July 2021 to present.

Alchem Laboratories
Chief Medical Officer

This position was as a consultant, but then briefly as an employee. Consulting for Alchem and/or its CEO: 2012 –2019. CMO 11/2019 to 4/2020.

- Led a high through-put screening and research team for drug development 2019-2020.
- Dr. Malone began modeling and focusing on the Plpro (papain-like protease) and Mpro (main protease) of then novel coronavirus (now SARS-CoV-2) using computational tools including Modeller to generate homology-modeled crystal structures for the SARS-CoV-2 Plpro and Mpro. Which generated a candidate list of repurposed drugs active against COVID-19, which was reduced

to a few candidates, based on binding sites, safety, licensure, efficacy, bioavailability of drug candidates.
- Led the discovery and early development of famotidine for the Treatment of COVID-19.
- Technical Lead/writer for funded full proposal under BAA-18-100-SOL-00003 Amendment 15 entitled: "A Multi-site, Randomized, Double-Blind, Multi-Arm Historical Control, Comparative Trial of the Safety and Efficacy of Hydroxychloroquine, and the Combination of Hydroxychloroquine and Famotidine for the Treatment of COVID-19 in Hospitalized Adults."
- Developed and wrote initial clinical trial design for a comparative trial of the safety and efficacy of hydroxychloroquine, and the combination of hydroxychloroquine and famotidine for the treatment of COVID-19 in hospitalized adults.

Atheric Pharmaceutical, LLC
CEO, and Co-founder.
Feb 2016-Dec 2017. Atheric™ Pharmaceutical LLC was a biopharmaceutical company focused on the rapid development and commercialization of re-purposed drugs to prevent and treat Zika and other Flavivirus disease. Optimization of high through-put screening techniques for anti-viral drug development.

Kennesaw State University
Adjunct Associate Professor 2009-2013

Beardsworth Consulting Group, Inc
Medical Director, Vaccines (RW Malone MD, LLC under contract to Beardsworth)
2010-2013
Dr. Malone functioned as the in-house medical vaccine expert for medical monitoring and Scientific Liaison
- Medical liaison to investigator sites including oversight of clinical monitoring
- Provided medical monitoring input including CRF review, 24x7 accessibility to site personnel, assess enrollment waiver requests, SAE review, etc.
- Safety Officer and Medical Representative on project teams
- Medical consultant to clients
- Business development/proposal writing/government contracting

Solvay Pharmaceuticals, Inc (currently Abbvie)
Director, Clinical Development & Medical Affairs, Influenza 2006-2008
Led an extended clinical team (both internal and CRO components), providing project and clinical trials management oversight, serving as primary author on clinical protocols, strategic documents including clinical development plans, DSMB/SMC charters, and all clinical documents required to support IND filing. Support and review of outcomes including safety data assessment
Generated and managed cost projections and budgetary oversight, providing strategic management and serving as a communication hub for clinical aspects of a $300 million USD federal contract to develop and license a cell-based influenza vaccine
Solvay's US Government contract for cell-based influenza vaccine was terminated around the end of 2007. At which point the cell-based influenza vaccine project was dissolved.

Summit Drug Development Services
Senior Medical Director 2005-2006

Directed due diligence assessments and strategic drug development planning and prepared regulatory submissions and implemented, monitored, and analyzed clinical trials for clients (oncology, vaccines, biologicals, cell/stem cell therapies). Primary author of three pIND, two IND, an Appendix M submission. Served as proposal manager and primary author for a 129M USD federal contract submission focused on pandemic influenza.

AERAS Global TB Vaccine Foundation

Director, Business Development and Program Management 2004-2005

Initially serving as consultant, provided leadership primarily focused on tuberculosis vaccine development and proposal development to NGO (B&M Gates), USG (CDC, NIH, DoD).

Dynport Vaccine Company, LLC

Associate Director, Clinical Research 2002-2003

- Served as liaison between product development teams and clinical research support groups.
- Prepared planning documents and product development plans.
- Participated in and supported safety review and assessment of smallpox vaccine product.
- Identified new technologies relevant to product development teams, facilitating integration of same in product development plans.
- Created documents for clinical trials including investigator brochures. Prepared proposal solicitations, technical review of subcontractor proposals. Performed technical review of potential subcontractors, new technologies.
- Assisted business development group in strategic evaluation and planning concerning new business opportunities and managed in-house Publication.

Intradigm, Corp

Co-Founder (one of three co-founders), CSO, Board of Director Member 2000-2001

Intradigm was a biotechnology company that develops gene therapeutic technology based on RNA interference. Intradigm merged with Silence Technologies in 2009 and the merged company is now publicly traded. Silence Technologies is involved in developmental research of targeted RNAi therapeutics for the treatment of serious diseases.

Dr. Malone co-founded and helped to secure $2.3 million in V.C. funding, including monies from the Novartis Venture Fund, ETP Venture Capital Fund and the State of Maryland. Performed facilities set-up, infrastructure set-up and Intellectual Property Development. Business and technology development planning, including in-depth business and scientific plan.

Uniformed Services University of the Health Sciences

Dept of Surgery, Clinical Breast Care Program (CBCP) through the Henry M. Jackson Foundation
Adjunct Associate Professor

Chief of Laboratory Science and Director of Tissue Banking 2000-2001

- Worked closely with architect firm to design space, set-up laboratory facilities for the Clinical Breast Care Project, including new facilities design (tissue banking facilities, laboratory, animal rooms, animal surgical suite, office suites) at USUHS and Windber Medical Center, PA
- Hired faculty, technicians, staff for CBCP at both sites, including writing and initiating job descriptions, job interviews, hiring decisions, set-up for re-locations
- Laboratory Supervisor: Tissue banking immunology, cell culture, gene transfer, genetic vaccination research, animal research.

University of Maryland, Baltimore School of Medicine, Dept. of Pathology
Assistant Professor 1997-2000
Set-up and ran successful research laboratory in immunology (genetic vaccination) and gene transfer.

University of California, Davis Department of Medical Pathology
1991-1997
Assistant Professor 1993-1997
Director and Founder, Gene Therapy Program (pulmonary, dermal, heart, liver, mucosal and parenteral vaccines).
Research Fellow, Pathology Resident 1991-1993

Vical, Inc
Research Scientist 1989

- Set up Vical's molecular biology laboratory.
- Initiated and carried out research in non-viral gene therapy and DNA vaccination.
- Inventor of "naked DNA" gene therapy. (see issued patents for details).
- Inventor of DNA vaccination (see issued patents below for details).
- Inventor of "mRNA" gene therapy. Salk institute.
- Inventor of mRNA vaccination. Salk institute.
- Inventor of "mRNA as a drug" or "transient gene therapy", terms both coined by Dr. Malone. Salk Institute.

LICENSURE / CERTIFICATIONS
Physician and Surgeon, State of Maryland License 1997-present. #DOO55466

BOARD OF DIRECTOR POSITIONS:
Discovery Cure, Inc. Founding Board of Director. 2018-2020
Epivax, Scientific Advisory Board, 2012-2019.

EDUCATION

- **HARVARD MEDICAL SCHOOL** *Global Clinical Scholars Research Training Program (fellowship)* A year-long comprehensive program that combines on-site (London, Boston) and distance learning, with an average of 15h per week lecture and practicum exercises. 2015-2016. Graduation with distinction (top 5% of graduating class).

- **UNIVERSITY OF CALIFORNIA, DAVIS:** RESEARCH FELLOWSHIP, 1992 – 1993
  Postgraduate Fellowship Award

- **UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER**: 1992
  Clinical Pathology Internship

- **NORTHWESTERN UNIVERSITY MEDICAL SCHOOL**: 1991
  Doctor of Medicine

- **UNIVERSITY OF CALIFORNIA, SAN DIEGO**: 1988
  Master of Science, Biology

- **UNIVERSITY OF CALIFORNIA, DAVIS**: 1984
  Bachelor of Science, Biochemistry

TEACHING EXPERIENCE

Kennesaw State University
Associate Professor:
BTEC 4490 Experimental Design and Analysis (2009): Survey course focused on advanced product development and regulatory aspects of biotechnology and vaccines products.
University of Maryland, Medical School
Assistant Professor:
Fundamentals of Molecular Biology (Graduate Course, Winter 2000)
Host defenses and Infectious Diseases, small group instructor Year 2 Medical School core curriculum. 1998, 1999
University of California, Davis
Assistant Professor:
MD 410A/410B. General Systemic Pathology (1992, 1993, 1994, 1995, 1996)
PTX 202. Principles of Pharmacology and Toxicology-Lecturer (1995, 1996)
BCM 214-414. Molecular Medicine-Lecturer (1995, 1996)
IM 295 Cytokines-Lecturer (1996), IDI 280. Molecular Basis of Disease-Lecturer (1996)
University of California, San Diego
Biology 111. Cell Biology (Fall 1988). Teaching Assistant under Dr. M. Montal
Biology 123. Embryology laboratory (Spring 1988). Teaching Assistant under Dr. C.Holt
Santa Barbara City College
Computer Laboratory (Spring 1981) Teaching Assistant

PROFESSIONAL OFFICES AND MEMBERSHIPS

- Royal Society of Medicine, Fellow 2021-present.
- Harvard Medical School Alumni, 2016- present.
- American Society of Tropical Medicine and Hygiene Member (ASTMH): 2016-2018.
- Virginia Bio: 2016-2018
- IEEE Genomics and Bioinformatics Working Group Member: 2002
- Northern Virginia Technology Council BioMedTech Committee: Co-chair: 2002 – 2003
- Intradigm, Corp. – a new start-up from Novartis, Inc.: Scientific Advisory Board: 2000 – 2001
- Novartis, Inc. (GTI/Systemix & Pharmacokinetics): Scientific Advisory Board and External Portfolio Reviewer: 1999 – 2001
- University of Maryland, Medical School: Pathology Education Policy Committee: 1999 – 2000

- UC Davis:
  - Education Policy Committee Graduate Group in Comparative Pathology: 1996 – 1/1997
  - Member, Biochemistry and Molecular Biology Graduate Group: 1993 – 1/1997
  - Member, Comparative Pathology Graduate Group: 1995 – 1/1997
- Boehringer Mannheim: Scientific Advisory Board: 1992 – 1993

EDITORIAL BOARDS

- Topic Editor, Frontiers in Pharmacology (Respiratory Pharmacology): "Treating COVID-19 with Currently Available Drugs," 2020-2021.
- Editor-In-Chief, Journal of Immune Based Therapies and Vaccines. 2009 – 2012, Editor: 2012.
- Gene Therapy/Molecular Biology International Society. 1997 – 2014.
- Reviewer for: Numerous peer-reviewed journals on infectious disease, public health 2016 to present.
- Nucleic Acids Research: 2001 – 2002.
- Molecular Therapy: 1999 – 2001.

ACADEMIC HONORS

- Harvard Medical School, Global Clinical Scholar Post Graduate: graduation with distinction (top 5% of graduating class).
- "DNA Vaccine" Recognizes Robert W. Malone, MD, MS, 2013.
- Trainee Investigator Award, American Federation for Clinical Research: 1993.
- Bank of America – Giannini Foundation Medical Research Fellow: 1992 – 1993.
- Henry Christian Award for Excellence in Research, American Federation for Clinical Research: 1992.
- UCDMC Medical Scholars Grant: 1992 – 1993.
- DNA and RNA Transfection and Vaccination (Abstract). First Place, Northwestern AOA Research Symposium Competition for Medical Students: 1989.
- USPHS Pre-Doctoral Fellowship: 1986 – 1988.
- San Diego Supercomputer Grant for RNA Structure Modeling: 1988.
- Northwestern University MD/ PhD Scholarship: 1984 – 1986.
- Dean's List, UC Davis: 1982 – 1984.
- President's Undergraduate Fellowship Grant for Investigation of Oncogene Expression in Breast Tumor Tissue: 1983 – 1984.
- Edmonson Summer Fellowship, Department of Pathology, UC Davis Medical School: 1984.

PATENTS ISSUED:

1. Lipid-mediated polynucleotide administration to deliver a biologically active peptide and to induce a cellular immune response (includes mRNA vaccination). Assigned to Vical, Inc and licensed to Merck. No. 7,250,404, date of issue: 7/31/07. Priority date 3/21/1989.

2. Lipid-mediated polynucleotide administration to reduce likelihood of subject's becoming infected (includes mRNA vaccination).. Assigned to Vical, Inc and licensed to Merck. US Pat. Ser. No. 6,867,195 B1, date of issue: 3/15/05. Priority date 3/21/1989.

3. Generation of an immune response to a pathogen (includes mRNA vaccination). Assigned to Vical, Inc and licensed to Merck. US Pat. Ser. No. 6,710,035, date of issue: 3/23/04. Priority date 3/21/1989.

4. Expression of exogenous polynucleotide sequences in a vertebrate, mammal, fish, bird or human (includes mRNA vaccination). Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 6,673,776, date of issue: 1/6/04. Priority date 3/21/1989.

5. Methods of delivering a physiologically active polypeptide to a mammal (includes mRNA vaccination). Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 6,413,942, date of issue: 7/2/02. Priority date 3/21/1989.

6. Induction of a protective immune response in a mammal by injecting a DNA sequence (includes mRNA). Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 6,214,804, date of issue: 4/10/01. Priority date 3/21/1989.

7. DNA vaccines for eliciting a mucosal immune response (includes mRNA). US Pat. Ser. No. 6,110,898, date of issue: 8/29/00. Priority date 1996.

8. Formulations and methods for generating active cytofectin: polynucleotide transfection complexes. US Pat. Ser. No. 5,925,623 7/20/99.

9. Cationic Transport Reagents. US Pat. Ser. No. 5,892,071 issued 4/06/99.

10. Polyfunctional cationic cytofectins, formulations and methods for generating active cytofectin: polynucleotide transfection complexes. US Pat. Ser. No. 5,824,812 issued 10/20/98.

11. Cationic Transport Reagents. US Pat. Ser. No. 5,744,625 issued 4/28/98.

12. Generation of antibodies through lipid mediated DNA delivery. Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 5,703,055, date of issue: 12/30/97. Priority date 3/21/1989.

13. Induction of a protective immune response in a mammal by injecting a DNA sequence (includes mRNA). Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 5,589,466, date of issue: 12/31/96. Priority date 3/21/1989.

14. Delivery of exogenous DNA sequences in a mammal (includes mRNA). Assigned to Vical, Inc, licensed to Merck. US Pat. Ser. No. 5,580,859, date of issue: 12/3/96. Priority date 3/21/1989.

15. Cationic Transport Reagents. US Pat. Ser. No. 5,527,928, date of issue: 6/18/96.

Of note: Cationic Lipid-Mediated RNA and DNA Transfection ("RNA as a Drug). 1988 patent application, Salk institute assignee, patent abandoned without inventor permission or knowledge. Inventor: Robert Malone. Available upon request.

PUBLICATIONS (selected)

COVID-19 Disease, Women's Predominant Non-Heparin Vaccine-Induced Thrombotic Thrombocytopenia and Kounis Syndrome: A Passepartout Cytokine Storm Interplay. Kounis, N.G.; Koniari, I.; … Malone, R.W. *Biomedicines* 2021, *9*, 959. https://doi.org/10.3390/biomedicines9080959

Famotidine and Celecoxib COVID-19 Treatment Without and With Dexamethasone; Retrospective Comparison of Sequential Continuous Cohorts, Submitted to Nature, Scientific Reports, May 2021. Robert W Malone, Kevin M Tomera, Leo Egbujiobi, Joseph K Kittah
Preprint at Research Square https://www.researchsquare.com/article/rs-526394/v1

More Than Just Heartburn: Does Famotidine Effectively Treat Patients with COVID-19? Malone RW. Dig Dis Sci. 2021 Feb 24:1–2. doi: 10.1007/s10620-021-06875-w. PMID: 33625612; PMCID: PMC7903029.

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms.
Malone RW, et. al. Frontiers in Pharmacololgy, 23 March 2021. https://doi.org/10.3389/fphar.2021.633680

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms.
Malone RW, et al DO.Res Sq. 2020 Jun 22:rs.3.rs-30934. doi: 10.21203/rs.3.rs-30934/v2. Preprint.PMID: 32702719 https://www.researchsquare.com/article/rs-30934/v2 Cited in 26 articles.

Hospitalized COVID-19 Patients Treated With Celecoxib and High Dose Famotidine Adjuvant Therapy Show Significant Clinical Responses (July 8, 2020). Tomera, K, Malone, R and kittah, J.
Available at SSRN: https://ssrn.com/abstract=3646583 or http://dx.doi.org/10.2139/ssrn.3646583

Medical Countermeasures Analysis of 2019-nCoV and Vaccine Risks for Antibody-Dependent Enhancement (ADE). Ricke, D.O.; Malone, R.W. Preprints 2020, 2020030138 (doi: 10.20944/preprints202003.0138.v1). May, 2020
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3646583

Molecular evolution of Zika virus as it crossed the Pacific to the Americas. Schneider AB, Malone RW, et al. Cladistics. 2017; 12: 10.1111/cla.12178

Zika Virus: Medical Countermeasure Development Challenges. Malone RW, et al. PLoS Negl Trop Dis. 2016;10(3):e0004530.

Zika Fetal Neuropathogenesis: Etiology of a Viral Syndrome. Klase ZA, Khakhina S, Schneider Ade B, Callahan MV, Glasspool-Malone J, Malone R. PLoS Negl Trop Dis. 2016;10(8):e0004877.

Antibody mediated epitope mimicry in the pathogenesis of Zika virus related disease. Homan J, Malone RW, et al. BioRxiv. 2016.

Making vaccines "on demand": a potential solution for emerging pathogens and biodefense? De Groot AS, Einck L, Moise L, Chambers M, Ballantyne J, Malone RW Hum Vaccin Immunother. 2013;9(9):1877-84.

Electroporation enhances transfection efficiency in murine cutaneous wounds. Byrnes CK, Malone RW, et al. Wound Repair Regen. 2004;12(4):397-403.

DNA transfection of macaque and murine respiratory tissue is greatly enhanced by use of a nuclease inhibitor. Glasspool-Malone J, …, Malone RW. J Gene Med. 2002;4(3):323-2.

Marked enhancement of macaque respiratory tissue transfection by aurintricarboxylic acid. Glasspool-Malone J, …, Malone RW. Gene Med. 2002;4(3):323-2.

Enhancing direct in vivo transfection with nuclease inhibitors and pulsed electrical fields. Glasspool-Malone J, Malone RW. In Gene Therapy Methods: Methods Enzymol. 2002;346:72-91

Cutaneous transfection and immune responses to intradermal nucleic acid vaccination are significantly enhanced by in vivo electropermeabilization. Drabick JJ, Glasspool-Malone J, …, Malone RW. Mol Ther. 2001;3(2):249-55.

Theory and in vivo application of electroporative gene delivery. Somiari S, Glasspool-Malone J, … Malone RW. Mol Ther. 2000;2(3):178-87.

Nucleic acid vaccination with a single SIV can protect rhesus macaques from oral challenge with pathogenic SIVMAC239. Gary Rhodes, … Robert Malone, et al. *Journal of Medical Primatology* 29.3-4 (2000).

Efficient nonviral cutaneous transfection. Glasspool-Malone J, …, Malone RW. Mol Ther. 2000;2(2):140-6. Citations:138 articles.

Transfer and expression of foreign genes in mammalian cells. Colosimo A, …, Malone RW, et al. Biotechniques. 2000;29(2):314-8, 20-2, 24 passim.

Specific inhibition of macrophage TNF-alpha expression by in vivo ribozyme treatment. Kisich KO, Malone RW, …, Erickson KL. J Immunol. 1999;163(4):2008-16.

Marked enhancement of direct respiratory tissue transfection by aurintricarboxylic acid. Glasspool-Malone J, Malone RW. Hum Gene Ther. 1999;10(10):1703-13

Developing dendritic cell polynucleotide vaccination for prostate cancer immunotherapy. Berlyn KA, …, Malone RW J Biotechnol. 1999;73(2-3):155-79

Models of Cationic Liposome Mediated Transfection. Gene Therapy and Molecular Biology. Ahearn A, Malone RW. Vol 4. Gene Therapy and Molecular Biology 1999;4

Feline dendritic-like cells: Isolation, culture, and genetic modification using monocytic precursors. Malone, J. G., Watts, T. L., Hale, A., & Malone, R. W. (1998, January). In *JOURNAL OF LEUKOCYTE BIOLOGY* (pp. 63-63): FEDERATION AMER SOC EXP BIOL.

Mucosal immune responses associated with polynucleotide vaccination. Malone JG, …, Malone RW. Behring Inst Mitt. 1997(98):63-72

Delivery of exogenous DNA sequences in a mammal. P Felgner, …, R Malone, D Carson. Biotechnology Advances. 1997 15 (3-4), 763-763

Cationic lipid-mediated gene delivery to murine lung: correlation of lipid hydration with in vivo transfection activity. Bennett MJ, …, Malone RW, Nantz MH. J Med Chem. 1997;40(25):4069-78

Improved method for the removal of endotoxin from DNA. Montbriand PM, Malone RW. J Biotechnol. 1996;44(1-3):43-6.

Toxicity of cationic lipid-ribozyme complexes in human prostate tumor cells can mimic ribozyme activity.Freedland SJ, Malone RW, et al. Biochem Mol Med. 1996;59(2):144-53

Considerations for the design of improved cationic amphiphile-based transfection reagents. Bennett MJ, …, Malone RW. Journal of Liposome Research 1996;6(3):545-65

Escherichia coli beta-glucuronidase and Photinus pyralis luciferase reporter. Ayar, S. F., & Malone, R. W. (1996, November). In *CLINICAL CHEMISTRY* (Vol. 42, No. 11, pp. 35-35).

Structural and functional analysis of cationic transfection lipids: the hydrophobic domain. Balasubramaniam RP, …, Malone RW. Gene Ther. 1996;3(2):163-72..

The counterion influence on cationic lipid-mediated transfection of plasmid DNA.Aberle AM, Bennett MJ, Malone RW, Nantz MH. Biochim Biophys Acta. 1996;1299(3):281-3

Direct gene transfer into mouse muscle in vivo. N Shafee, ..., RW Malone, et al. International Journal of Virology 2 (1), 33-38

A flexible approach to synthetic lipid ammonium salts for polynucleotide transfection. MJ Bennett, RW Malone, MH Nantz. Tetrahedron letters 36 (13), 2207-2210

Tfx-50 Reagent, a new transfection reagent for eukaryotic cells. Schenborn E, …, Malone RW, et al. 1995

Hepatic gene expression after direct DNA injection. Hickman MA, Malone RW, et al. Advanced Drug Delivery Reviews. 1995;17(3):265-71

Ribozyme and messenger-RNA delivery using cationic liposomes RW MALONE 1995/1/5 Conference JOURNAL OF CELLULAR BIOCHEMISTRY Pages 206 Publisher WILEY-LISS

Cholesterol enhances cationic liposome-mediated DNA transfection of human respiratory epithelial cells. Bennett MJ, …, Malone RW. Biosci Rep. 1995;15(1):47-53

Dexamethasone enhancement of gene expression after direct hepatic DNA injection. Malone RW, et al. J Biol Chem. 1994;269(47):29903-7

Gene expression following direct injection of DNA into liver. Hickman MA, Malone RW, et al. Hum Gene Ther. 1994;5(12):1477-83.

Cationic liposome-mediated RNA transfection. Dwarki VJ, Malone RW, Verma IM. Methods Enzymol. 1993;217:644-54.

Successful gene transfection of respiratory epithelium invitro using polyamine containing cationic lipids. CB Robinson, RW Malone, J Jessee, G Gebeyehu, R Wu AMERICAN REVIEW OF RESPIRATORY DISEASE 147 (4), A546-A546

Direct gene transfer into mouse muscle in vivo. Wolff JA, Malone RW, et al. Science. 1990;247(4949 Pt 1):1465-8.

Cationic liposome-mediated RNA transfection. Malone RW, Felgner PL, Verma IM. Proc Natl Acad Sci U S A. 1989;86(16):6077-81.

mRNA Transfection of cultured eukaryotic cells and embryos using cationic liposomes. Malone RW. Focus. 1989;11:61-8

High levels of messenger RNA expression following cationic liposome mediated transfection tissue culture cells. Malone R, Kumar R, Felgner P. NIH Conference: "Self-Cleaving RNA as an Anti-HIV Agent" (Abstract). Washington, DC June 1989.

A novel approach to study packaging of retroviral RNA by RNA transfection (Abstract). RW Malone, P. Felgner, I. Verma. RNA Tumor Viruses, May 17-18, 1988. Cold Spring Harbor

Mammary tumors in feral mice lacking MuMTV DNA. Gardner MB, Malone RW, …, Cardiff RD, et al. J Exp Pathol. 1985;2(2):93-8

Hyperplastic and neoplastic changes in the mammary glands of feral mice free of endogenous mouse mammary tumor virus provirus. Faulkin LJ, …, Malone RW, et al. J Natl Cancer Inst. 1984;73(4):971-82.

PUBLISHED ABSTRACTS: Over 50 published

CHAIRPERSON/ORAL PRESENTATIONS BY INVITATION: **Over 40 Invitations**
(Only the most recent events listed)

- Vaccines R&D, 2021. Keynote Speaker. September, 2021

- International Covid-19 Summit, Keynote speaker and chair. Rome, Italy, September, 2021

- Vaccines R&D, 2019. Keynote Speaker, Panel Moderator: Boston, MA. 18-20 November, 2019.

- Repurposing drugs for Infectious Disease Outbreaks. International Conference on Zika Virus. Washington, DC Feb 22-25, 2017 (Chairperson)

- Accelerated Discovery and Development of re-purposed licensed drugs for Zika virus outbreak antiviral prophylaxis and therapy. International Conference on Zika Virus. Washington, DC Feb 22-25, 2017. (Oral Presentation)

- Zika Virus: Accelerating Development of Medical Countermeasures by Re-purposing Licensed Drugs. Bridging the Sciences: Zika Virus. Emery, Atlanta, GA 1-3 May, 2016. (Oral Presentation)

- Speaker/Round table- Zika virus: Challenges for Medical Countermeasure Development. World Vaccine Conference. Washington, DC. 29-31 March, 2016.

- The World Health Organization (WHO) Consultation for Zika Virus: Research and Development. Presentation of Drug Development TPP. Geneva, Switzerland. 12-14 March, 2016. (Oral Presentation)

- Keynote Speaker: Ebola Vaccine in 12 months, Global Village, and the Need for Speed. Vaccines R&D, Baltimore, MD. 2-4 November, 2015. (Keynote Speaker)

- Current USG contracting Opportunities and Initiatives from the point of View of Vaccine Developers. World Vaccine Conference, Washington, DC. 24-26 March, 2014. (Oral Presentation)

- World Vaccine Conference, Washington, DC. 24-26 March, 2014 Preclinical and Clinical Vaccine Research. (Session Chair)

- PHEMCE Modeling Workshop "Operational Decision Making using Innovative Modeling, Analysis, and Visualization Tools", Sponsored by Deloitte. 2013 (Conference Co-Organizer and Coordinator/Oral Presentation)

- "Vaccine Production Strategies: Ensuring Alignment and Sustainability" The World Health Organization (WHO) Global Action Plan for Influenza Vaccines. Geneva, Switzerland. 12-14 July 2011 (Oral Presentation)

RECENT STUDY SECTIONS (selected):

- Accelerated COVID-19 Therapeutic Interventions and Vaccines:
  ACTIV Therapeutics Clinical Working Group, NIH. Invited Participant. June, 2020-present.
- Chairperson, NIH/NIAID/DMID Special Emphasis Panel, Development of Vaccines to Combat Antibiotic Resistant Bacteria September 2019.

- Chairperson, NIH/NIAID Special Emphasis Panel, December 2018.
- Reviewer, NIH/NIAID Special Emphasis Panel, December 2017.
- Chairperson and scientific reviewer for Department of Defense, U.S. Army Medical Research and Materiel Command, for "Congressionally Directed Medical Research Programs (DMRDP), 2012.
- Committee member and reviewer for NIH/NIAID Committee for Development of Technologies that Accelerate the Immune Response to BioDefense Vaccines. 2011
- Chair and reviewer for NIH/NIAID: Partnerships in Biodefense Immunotherapeutics. 2011
- NIH/NIAID Committee member and reviewer for Development of Technologies to Facilitate the Use of, and Response to Biodefense Vaccines," Special Emphasis panel. 2010
- Chairperson and scientific reviewer for NIH/NIAID Omnibus BAA 2017-1: Research Area 5 (N01) ZAI1-KP- M-C6 (Topic 5: Advanced Development of Vaccine Candidates for Biodefense and Emerging Infectious Diseases), September 2017.
- Scientific reviewer for NIH/NIAID Special Emphasis Panel/Scientific Review Group 2017/08 ZRG1 IMM-R (12) B (Non-HIV Microbial vaccines), June 2017.
- Chairperson and scientific reviewer for Department of Defense, U.S. Army Medical Research and Materiel Command, "CDMRP: Defense Medical Research & Development Program (DMRDP), 2012.
- Chairperson and scientific reviewer for NIH/NIAID Committee on Partnerships in Biodefense Immunotherapeutics, Fall 2011.
- Committee member and reviewer for NIH/ NIAID Committee for Development of Technologies that Accelerate the Immune Response to BioDefense Vaccines, Fall 2011.
- NIH/ NIAID Committee member and reviewer for Development of Technologies to Facilitate the Use of, and Response to Biodefense Vaccines," Special Emphasis panel, 2010.
- NIH Study Section K01 Breast Cancer Study Section: July 1997
- NIDDK Special Emphasis Panel Review Committee for Competing Continuation Program Project: April 1999 and April 1998
- NIAID Study Section "Innovative Grant Program for Approaches in HIV Vaccine Research": 1998

BOOKS AND BOOK CHAPTERS

- *Canary In a Covid World: How Propaganda and Censorship Changed Our World* Kindle Edition by Various Author, including Dr. Robert Malone (Author), 2023.

- *Lies my Government Told Me and the Better Future Coming.* Robert W. Malone, MD, MS. 447 pages. Skyhorse Publishing. 2022 (on multiple best seller lists). 2022.

- *Molecular Virology of COVID-19.* Glasspool-Malone, J, Malone RW. In "*COVID-19 for Health Care."* 2022.

- Malone RW. *"Present and Future Status of Gene Therapy.' Intro Chapter in Advanced Gene Delivery: From Concepts to Pharmaceutical Products*." Editor: Allain Rolland. Harwood Academic Pub. 1998, republished 2014.

- *Enhancing direct in vivo transfection with nuclease inhibitors and pulsed electrical fields***.** Glasspool-Malone J, Malone RW. In *Gene Therapy Methods: Methods Enzymol.* 2002;346:72-91

- Malone RW. *"Toxicology of non-viral gene transfer".* Editor, Walsh B. In*: "Non-Viral Therapeutics: Advances, Challenges and Applications for Self-Assembling Systems*." IBC's Biomedical Library Series. (1996) 4.1

NATIONAL NEWSPAPER ARTICLES

Sorry Facebook, forced universal vaccinations are not the answer
All the science should be considered, not censored
Washington Times, September 1, 2021.
By: Dr. Robert Malone and Peter Navarro
https://www.washingtontimes.com/news/2021/sep/1/sorry-facebook-forced-universal-vaccinations-are-n/

Biden team's misguided and deadly COVID-19 vaccine strategy
Vaccination 'arms race' could prove dangerous to the American public
Dr. Robert Malone and Peter Navarro,
Washington Times, August 5, 2021.
https://www.washingtontimes.com/news/2021/aug/5/biden-teams-misguided-and-deadly-covid-19-vaccine-/
Online and print editions

NATIONAL PODCASTS, BROADCASTS AND DOCUMENTARIES

Dr. Malone has been featured on many TV shows and podcasts, including Joe Rogan (after which Dr Malone's episode was the #1 podcast in the world), Fox News with Tucker Carlson, the War Room with Steve Bannon, Mercola, One America News, Glen Beck, Laura Ingraham, Epoch Times, News Max, Russia Times, The Dark Horse Studio and dozens more. Please search Spotify or Apple Podcasts ("Robert Malone"), as well as IMDB: Robert W. Malone (https://www.imdb.com/name/nm5374331/) for listings.

STATE, FEDERAL AND FOREIGN GOVERNMENT LEGISLATIVE TESTIMONY

Tennessee State Legislature 2021
Texas Senate, Health and Human Safety Committee, 2021
US Senate, Roundtable - COVID-19: A Second Opinion Hearing, Jan 2022 (https://rumble.com/vt62y6-covid-19-a-second-opinion.html)
Louisiana State Senate Health and Human Services Committee, 2022
Texas Senate, Health and Human Services Committee, 2022
US Senate, Senator Johnson Roundtable: COVID-19 Vaccines - What they are, how they work, and possible causes of injuries, Dec. 2022
Mexico Senate, April 2023
European Union (Parliament), Brussels May, 2023

Exhibit B

From: Arthur Kim, Esq.

Date: 9/7/23

Case: *Georgia Ringler v. The Scripps Research Institute*

San Diego Superior Court

Instructions for Robert W. Malone, M.D.

I. OUR LEGAL BASIS

California Government Code Section 12940 states:

It is an unlawful employment practice…

(l)(1) For an employer or other entity covered by this part…**to discharge a person from employment** or from a training program leading to employment, or to discriminate against a person in compensation or in terms, conditions, or privileges of employment **because of a conflict between the person's religious belief or observance and any employment requirement**, **unless the employer** or other entity covered by this part **demonstrates that it has explored any available reasonable alternative means of accommodating the religious belief or observance**, including the possibilities of excusing the person from those duties that conflict with the person's religious belief or observance or permitting those duties to be performed at another time or by another person, **but is unable to reasonably accommodate the religious belief or observance without undue hardship**, as defined in subdivision (u) of Section 12926, on the conduct of the business of the employer or other entity covered by this part.

(bold and underline emphasis added).

California Government Code Section 12926(u) states:

"Undue hardship" means an action requiring **significant difficulty or expense**, when considered in light of the following factors:

(1) The nature and cost of the accommodation needed.
(2) The overall financial resources of the facilities involved in the provision of the reasonable accommodations, the number of persons employed at the facility, and the effect on expenses and resources of the impact otherwise of these accommodations upon the operation of the facility.
(3) The overall financial resources of the covered entity, the overall size of the business of a covered entity with respect to the number of employees, and the number, type, and location of its facilities.

(4) The type of operations, including the composition, structure, and functions of the workforce of the entity.
(5) The geographic separateness or administrative or fiscal relationship of the facility or facilities.

(bold emphasis added).

II. OUR LEGAL THEORY

"Defendants violated Government Code Section 12940(l) by discriminating against Plaintiff in the terms, conditions, and privileges of employment and terminating Plaintiff's employment because of a conflict between Plaintiff's religious belief or observance and Defendants' employment requirement, ***even though a reasonable alternative means of accommodating the religious belief or observance was available***." Complaint for Damages at paragraph 22.

III. FACTS RE SCRIPPS' VACCINE MANDATE

According to Scripps:

- As of January 8, 2021:

  …we are seeing the ***increased spread of the virus*** throughout the broader community manifest on campus through our screening program. Indeed, Monday January 4th set a new single day record for us, when we reported ***7 new confirmed positives*** from amongst those that screened on campus. In addition, several employees have self-quarantined after being exposed to the virus while off-campus during the holidays. Unfortunately, we do not expect the vaccine to have a near-term impact on our on-campus operations (read below for more context). So at this time, we are reinforcing our message to all on-campus employees to remain vigilant on and off campus with rigorous social distancing, hygiene, and compliance with screening and daily certifications. (Exhibit 6, Defendants' Motion for Summary Judgment ("MSJ")) (bold, italic emphasis added)

- As of February 25, 2021:

  we are ***still identifying positive results*** via our regular SARS-CoV-2 screenings… (Exhibit 7, Defendants' MSJ) (emphasis added)

- As of March 30, 2021:

  nearly 70% of Scripps Research personnel regularly working on the La Jolla campus who participated in the recent survey had received ***at least one dose*** of a COVID-19 vaccine… (Exhibit 8, Defendants' MSJ) (emphasis added)

  And while nearly 5% of survey respondents reported having been diagnosed with COVID at some point over the past year, we are happy to share that our screening program has only picked up ***1 confirmed positive in the last month***." (Exhibit 8, Defendants' MSJ) (emphasis added)

  Daily COVID Certification amendment
  Once you have been fully vaccinated (and confirmed in REDCap) you ***no longer need to submit the Daily COVID Certification***. However, you must email covid19@scripps.edu if you become sick with COVID-19 symptoms or are directly exposed to someone you know to have COVID-19. (Exhibit 8, Defendants' MSJ) (bold, italic emphasis added)

  SARS-CoV-2 screening schedule
  Effective immediately, the institute is revising its twice-weekly screening requirement:
  - On-campus personnel who have ***not*** **yet been fully vaccinated** against COVID-19 must **complete SARS-CoV-2 screening once a week**.
  - Those who have been **fully vaccinated against COVID-19** only need to complete SARS CoV 2 screening **once per month**.

  (Exhibit 8, Defendants' MSJ)

- As of May 5, 2021:

  Based on data reported to REDCap, approximately ***65%*** of Scripps Research personnel currently working on the La Jolla campus have verified that they are ***fully vaccinated***. (Exhibit 9, Defendants' MSJ) (bold, italic emphasis added)

  Changes to Daily Health Certification – Fully vaccinated personnel are ***no longer required to complete the Daily Health Certification*** unless symptoms develop after a known exposure. Unvaccinated personnel must continue to completethe Daily Health Certification via REDCap before arriving on campus, and if symptoms develop after recently being on campus. (Exhibit 9, Defendants' MSJ) (bold, italic emphasis added)

  Revised SARS-CoV-2 screening – If you are fully vaccinated against COVID-19 and have uploaded your vaccination card via REDCap, *you no longer need to complete SARS-CoV-2 screens on campus*. (However, if you wish to voluntarily participate in screening, you may continue to do so.) If you are not fully

vaccinated, you must continue to complete SARS-CoV-2 screening each week. (Exhibit 9, Defendants' MSJ) (bold, italic emphasis added)

- As of June 16, 2021:

  More than ***84%*** of our Scripps Research California community report being ***fully vaccinated*** against COVID-19….
  Limited SARS-CoV-2 screening. If you are ***fully vaccinated*** against COVID-19 and have uploaded your vaccination card via REDCap, ***you should no longer complete SARS-CoV-2 screening on campus***. (Exhibit 10, Defendants' MSJ) (bold, italic emphasis added)

- As of July 26, 2021:

  More than ***89%*** of our La Jolla community has reported being ***fully vaccinated***…
  Regular Screening
  Weekly screening is still mandatory for unvaccinated individuals who spend time on campus. By request, we are making voluntary screening available again for those who are vaccinated. We will be increasing the availability of screening times to accommodate. The BCC screening location will be open **Mondays and Wednesday from 9 a.m. to 1 p.m.** Email covid19@scripps.edu to register for the screening, if you have not already. Book an appointment using this link…
  (Exhibit 12, Defendants' MSJ) (bold, italic emphasis added)

- As of August 6, 2021:

  Effective September 15, all personnel are required to be vaccinated against COVID-19. (Exhibit 14, Defendants' MSJ)

  The COVID-19 Vaccination Policy ("Policy") is implemented to help protect the health and safety of the Scripps Research community and reduce the risk that an individual on the Scripps Research campus has SARS-CoV-2 with the potential to transmit to others, consistent with current applicable federal, state, and local law.
  …
  Fully Vaccinated: Personnel are considered fully vaccinated two weeks after receiving: (a) the second dose in a two-dose COVID-19 vaccine series or a single dose COVID-19 vaccine. Vaccines must be FDA approved, have an emergency use authorization from the FDA, or, for persons vaccinated outside the United States, be listed for emergency use by the World Health Organization ("WHO"). (Exhibit 20, Defendants' MSJ)

- As of September 14, 2021:

  …we have made the difficult decision to terminate your position at Scripps Research effective September 15, 2021. (Exhibit 18, Defendants' MSJ)

According to Vice President of HR, Karen Hagenmiller:

- "***we had our own saliva test*** that we were providing for all of our employees, and we would – ***we would always back it up with a PCR test***. And so we were aware of people who had symptoms, tested negative, and then continued to have symptoms and were ultimately positive." Deposition transcript at page 28, lines 17-22.

- Q. Now, did you know at the time whether the testing would provide as good protection as vaccines?
  A. I was not aware.…

  Q. Sitting here today, are you aware of any discussion at Scripps about whether testing is as safe as a vaccine for COVID?

  A. I'm not.…

  Q. During the time that you were at Scripps as vice-president of HR, did you ever learn of a discussion about whether testing was as safe as the vaccine in protecting employees from COVID?

  A. Not that I recall.…

  Q. Did you ever see any study about whether testing was as safe as the vaccine in terms of protecting employees from COVID?…

  A. Not that I recall.…

  Q. …**Did the crisis management team ever compare the effectiveness of testing versus the vaccine with respect to COVID?**…

  A. Not that I recall.

  Deposition transcript at page 30 line 1 to page 32 line 7.

IV. FACTS RE GEORGIA RINGLER'S JOB DUTIES

Plaintiff was an events manager. See her testimony at Exhibit 2, Defendants' MSJ. See also her job description (Exhibit 5, Defendants' MSJ) and her performance review (Exhibit 15, Defendants' MSJ).

///

///

///

V. EXPERT OPINION REQUESTED

Question 1

Was there an alternative to vaccination of Plaintiff – *for example, daily PCR testing by Plaintiff and daily certification by Plaintiff regarding Covid symptoms* – that would have provided equivalent health and safety to the Scripps community?[1]

Question 2

Was this knowledge available on September 14, 2021?

VI. ADDITIONAL OPINION REQUESTED

According to document bates numbered P60 to P62, a fact sheet from the Charlotte Lozier Institute:

- The fetal cell line PER.C6 was used in the development or production of the Johnson & Johnson vaccine.
- The fetal cell line HEK293 was used in the testing of the Moderna vaccine.
- The fetal cell line HEK293 was used in the testing of the Pfizer vaccine.

Is this true?

[1] As detailed in the fact section above, beginning in or around May 5, 2021, Scripps no longer required the fully vaccinated to test for Covid or to provide daily certification regarding Covid symptoms.

Exhibit C

To: Arthur Kim, Esq.
Date: 03 October, 2023
Case: *Georgia Ringler v. The Scripps Research Institute*
San Diego Superior Court
From: Robert W. Malone, MD, MS
355 Hebron Valley Road
Madison, VA 22727

Hon. Mr. Kim

I have reviewed the documentation you have provided concerning the case of *Georgia Ringler v. The Scripps Research Institute,* currently pending in San Diego Superior Court.

I have been requested to provide sworn testimony as an expert witness in this case, based on my qualifications combined with my detailed experience in tracking the events, US Government communications, and having worked as a consultant to US DoD/DTRA and serving on the NIH ACTIV committee on behalf of US DoD/DTRA during the SARS-CoV-2 Coronavirus outbreak during 2021.

Question 1
Was there an alternative to vaccination of Plaintiff that would have provided equivalent health and safety to the Scripps community?

The Scripps community and The Scripps Research Institute (TSRI) had apparently implemented an employee vaccine mandate before the time of the employment termination of Ms. Ringler on September 14, 2021. As documented by the Washington Post on July 29, 2021 in the following two public disclosures relating to an internal CDC slide deck, it had become public knowledge that the vaccines available for the plaintiff Ms. Ringler to potentially use were leaky, and did not prevent infection, replication, and spread of SARS-CoV-2 virus in vaccinated persons. "Leaky" is a common technical term in vaccinology meaning that a vaccine recipient is prone to "breakthrough infections". Therefore, based on these data, knowledge and documentation were available to the general public including TSRI on or before July 29, 2021 that these available vaccines would not and could not prevent infection or spread of SARS-CoV-2 and COVID disease. Furthermore, based on this publicly disclosed CDC slide deck, even if 100% of TSRI employees were so vaccinated and all employed CDC best practices in use of particle masks, "herd immunity" or collective protection from SARS-CoV-2 infection, replication, transmission and associated COVID-19 disease could not be prevented by use of these vaccine products.

For further corroborating details, please see the following external resources:

Washington Post- July 29, 2021 at 8:58 p.m. EDT
'The war has changed': Internal CDC document urges new messaging, warns delta infections likely more severe. The internal presentation shows that the agency thinks it is struggling to communicate on vaccine efficacy amid increased breakthrough infections
By Yasmeen Abutaleb, Carolyn Y. Johnson and Joel Achenbach
https://www.washingtonpost.com/health/2021/07/29/cdc-mask-guidance/

Washington Post
Read: Internal CDC document on breakthrough infections
Updated Jul 30, 2021 at 10:15 AM
An internal CDC document urges officials to "acknowledge the war has changed" and improve the public's understanding of breakthrough infections.
(Provides copy of official CDC slide deck)
https://www.washingtonpost.com/context/cdc-breakthrough-infections/94390e3a-5e45-44a5-ac40-2744e4e25f2e/

On August 27, 2021, the CDC journal Morbidity and Mortality Weekly Report (MMWR) published the results of a large study assessing "Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021" which provides an estimate of the effectiveness (through August 14, 2021) of all COVID-19 vaccines available in USA to TSRI employees. The CDC study also examined whether vaccine effectiveness differs for adults with increasing time since completion of all recommended vaccine doses. In the abstract summarizing this study, the **CDC noted that SARS-CoV-2 B.1.617.2 (Delta) variant predominance (the predominant SARS-CoV-2 strain circulating at the time of the plaintiff's termination) coincided with an increase in reported COVID-19 vaccine breakthrough infections.**

MMWR Morbidity and Mortality Weekly. 2021 Aug 27;70(34):1167-1169. doi: 10.15585/mmwr.mm7034e4.
Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021
Ashley Fowlkes, Manjusha Gaglani, Kimberly Groover et al. HEROES-RECOVER Cohorts

In this MMWR publication, with CDC staff as lead authors, the study reports that:
"During Delta variant–predominant weeks at study sites, 488 unvaccinated participants contributed a median of 43 days (IQR = 37–69 days; total = 24,871 days) with 19 SARS-CoV-2 infections (94.7% symptomatic); 2,352 fully vaccinated participants contributed a median of 49 days (IQR = 35–56 days; total = 119,218 days) with 24 SARS-CoV-2 infections (75.0% symptomatic). Adjusted ***VE during this Delta predominant period was 66% (95% CI = 26%–84%) compared with 91% (95% CI = 81%–96%) during the months preceding Delta predominance****."*

Delta was the dominant SARS-CoV-2 variant at the time plaintiff Ms. Ringler's employment with TSRI was terminated, but at that time, the Delta variant was beginning to be displaced by the Omicron variant. In a preprint originally posted on the MedRxIV server on January 01, 2022, and subsequently published in JAMA Network on September 22, 2022, it was reported that receipt of 2 doses of COVID-19 vaccines was not protective against Omicron. In that study, vaccine effectiveness against Omicron was measured at 37% (95%CI, 19-50%) ≥7 days after receiving an mRNA vaccine for the third dose.

Effectiveness of COVID-19 vaccines against Omicron or Delta infection
Sarah A. Buchan, Hannah Chung, Kevin A. Brown et al.
medRxiv 2021.12.30.21268565; doi: https://doi.org/10.1101/2021.12.30.21268565

Therefore, depending on whether a hypothetical TSRI employee such as the plaintiff were to be infected with either the Delta or Omicron variants of SARS-CoV-2, these data from that time period indicate the vaccine effectiveness of the mRNA vaccines for COVID available at that time would be in the range of 66% (44% failure to protect) to "not effective" (complete failure to protect) for prevention of infection after two doses.

In contrast, if the plaintiff Ms. Ringler and TSRI were to have employed PCR or rapid antigen testing every three days in accordance with the NIH-published study entitled "Longitudinal Assessment of Diagnostic Test Performance Over the Course of Acute SARS-CoV-2 Infection", then the TSRI would have benefitted from an approximately 98% sensitivity for detecting infection in staff including Ms. Ringler.

Quoting from the study conclusions:
"RT-qPCR tests are more effective than antigen tests at identifying infected individuals prior to or early during the infectious period and thus for minimizing forward transmission (given timely results reporting). All tests showed >98% sensitivity for identifying infected individuals if used at least every 3 days. Daily screening using antigen tests can achieve approximately 90% sensitivity for identifying infected individuals while they are viral culture positive."

Therefore, if Plaintiff Ms. Ringler were to have been provided the opportunity to certify thrice weekly, in accordance with the NIH protocol published 15 September 2021, or even daily testing as Plaintiff had indicated willingness to perform, and by Plaintiff demonstrating evidence of the absence or presence of SARS-CoV-2-derived nucleic acids or clinical COVID symptoms, coupled to compliance with appropriate quarantine procedures including

working from home and/or avoidance of TSRI workplace(s) in the event of evidence of SARS-CoV-2 nucleic acid or COVID symptoms, this would have provided **clearly superior protection of other members of the TSRI community** from any infection which plaintiff Ms. Ringler might have contracted. Based on these NIH data, such testing would have provided at least 98% sensitivity in detection of an infection, in contrast to vaccination providing somewhere in the range of 66% to 37% (after three doses) to virtually no protection against SARS-CoV-2 infection.

Longitudinal Assessment of Diagnostic Test Performance Over the Course of Acute SARS-CoV-2 Infection
Rebecca L Smith, Laura L Gibson, Pamela P Martinez et al.
The Journal of Infectious Diseases, Volume 224, Issue 6, 15 September 2021, Pages 976–982,
https://doi.org/10.1093/infdis/jiab337

Finally, based on the information known to both CDC and the public as of July 30, 2021, the cited literature, and subsequent additional peer reviewed literature including that noted above concerning the leakiness of the available vaccines, it is highly likely that rigorous examination of TSRI employee health records will reveal multiple examples of vaccinated TSRI employees who contracted SARS-CoV-2 infection with or without COVID disease despite being fully compliant with TSRI vaccination policy, which would clearly demonstrate the failure of the TSRI proposed public health measures to achieve the objective of eliminating the risk of SARS-CoV-2 infection or COVID disease in TSRI employees and other persons associated with TSRI via a vaccination requirement.

Question 2
Was this knowledge available on September 14, 2021?

As documented, this knowledge was available to the general public and TSRI on or before July 30, 2021, well before September 14, 2021

Additional opinion
According to document bates numbered P60 to P62, a fact sheet from the Charlotte Lozier Institute:
•The fetal cell line PER.C6 was used in the development or production of the Johnson & Johnson vaccine.
•The fetal cell line HEK293 was used in the testing of the Moderna vaccine.
•The fetal cell line HEK293 was used in the testing of the Pfizer vaccine.

These are true statements based on the cited fact sheet as well as multiple source of information widely distributed and generally known to the public and TSRI.

This concludes my expert testimony regarding the two questions which have been posed.

Sincerely

Robert W. Malone, MD, MS
Maryland Board of Health licensed Physician and Surgeon #DOO55466

Exhibit D

Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021

Ashley Fowlkes, ScD[1]; Manjusha Gaglani, MBBS[2]; Kimberly Groover, PhD[3]; Matthew S. Thiese, PhD[4]; Harmony Tyner, MD[5]; Katherine Ellingson, PhD[6]; HEROES-RECOVER Cohorts

On August 24, 2021, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

During December 14, 2020–April 10, 2021, data from the HEROES-RECOVER Cohorts,* a network of prospective cohorts among frontline workers, showed that the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines were approximately 90% effective in preventing symptomatic and asymptomatic infection with SARS-CoV-2, the virus that causes COVID-19, in real-world conditions (*1,2*). This report updates vaccine effectiveness (VE) estimates including all COVID-19 vaccines available through August 14, 2021, and examines whether VE differs for adults with increasing time since completion of all recommended vaccine doses. VE before and during SARS-CoV-2 B.1.617.2 (Delta) variant predominance, which coincided with an increase in reported COVID-19 vaccine breakthrough infections, were compared (*3,4*).

Methods for the HEROES-RECOVER Cohorts have been published previously (*1,2,5*). Health care personnel, first responders, and other essential and frontline workers in eight U.S. locations across six states were tested weekly for SARS-CoV-2 infection by reverse transcription–polymerase chain reaction (RT-PCR)† and upon the onset of any COVID-19–like illness. Weeks when the Delta variant accounted for ≥50% of viruses sequenced, based on data from each respective location, were defined as weeks of Delta variant predominance. Vaccination was documented by self-report and verified by provision of vaccine cards or extraction from electronic medical records or state immunization registries. Among 4,217 participants, 3,483 (83%) were vaccinated; 2,278 (65%) received Pfizer-BioNTech, 1,138 (33%) Moderna, and 67 (2%) Janssen (Johnson & Johnson) COVID-19 vaccines. Cox proportional hazards models were used to calculate ratios of unvaccinated to fully vaccinated (≥14 days after receipt of all recommended COVID-19 vaccine doses) infection rates, adjusted for occupation, site, and local viral circulation (*6*), and weighted for inverse probability of vaccination using sociodemographic characteristics, health information, frequency of close social contact, and mask use. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.§

During the 35-week study period, 4,136 participants with no previous laboratory-documented SARS-CoV-2 infection contributed a median of 20 unvaccinated days per participant (interquartile range [IQR] = 8–45 days; total = 181,357 days), during which 194 SARS-CoV-2 infections were identified; 89.7% of these infections were symptomatic. A total of 2,976 participants contributed a median of 177 fully vaccinated days (IQR = 115–195 days; total = 455,175 days) with 34 infections, 80.6% of which were symptomatic. Adjusted VE against SARS-CoV-2 infection was 80% (95% confidence interval [CI] = 69%–88%). The VE point estimate was 85% among participants for whom <120 days had elapsed since completion of full vaccination compared with 73% among those for whom ≥150 days had elapsed; however the VE 95% CI were overlapping, indicating the difference was not statistically significant (Table).

During Delta variant–predominant weeks at study sites, 488 unvaccinated participants contributed a median of 43 days (IQR = 37–69 days; total = 24,871 days) with 19 SARS-CoV-2 infections (94.7% symptomatic); 2,352 fully vaccinated participants contributed a median of 49 days (IQR = 35–56 days; total = 119,218 days) with 24 SARS-CoV-2 infections (75.0% symptomatic). Adjusted VE during this Delta predominant period was 66% (95% CI = 26%–84%) compared with 91% (95% CI = 81%–96%) during the months preceding Delta predominance.

During December 14, 2020–August 14, 2021, full vaccination with COVID-19 vaccines was 80% effective in preventing RT-PCR–confirmed SARS-CoV-2 infection among frontline workers, further affirming the highly protective benefit of full vaccination up to and through the most recent summer U.S. COVID-19 pandemic waves. The VE point estimates declined from 91% before predominance of the SARS-CoV-2 Delta

* Arizona Healthcare, Emergency Response and Other Essential Workers Surveillance Study (HEROES) conducted in Phoenix, Tucson, and other noncentrally located areas in Arizona; Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) conducted in Miami, Florida; Duluth, Minnesota; Portland, Oregon; Temple, Texas; and Salt Lake City, Utah.

† RT-PCR was conducted using the Quidel Lyra SARS-CoV-2 Assay (before November 2020) or TaqPath COVID-19 Combo Kit (Applied Biosystems) at the Marshfield Clinic Research Institute (Marshfield, WI).

§ 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect 241(d); 5 U.S.C. Sect 552a; 44 U.S.C. Sect 3501 et seq.

TABLE. Effectiveness of COVID-19 vaccines against any SARS-CoV-2 infection among frontline workers, by B.1.617.2 (Delta) variant predominance and time since full vaccination — eight U.S. locations, December 2020–August 2021

Period and vaccination status	No. of contributing participants*	Total no. of person-days	Median days (IQR)	No. of SARS-CoV-2 infections	Adjusted VE,† % (95% CI)
Full cohort to date					
Unvaccinated	4,136	181,357	20 (8–45)	194	N/A
Fully vaccinated§	2,976	454,832	177 (115–195)	34	80 (69–88)
14–119 days after full vaccination	2,923	284,617	106 (106–106)	13	85 (68–93)
120–149 days after full vaccination	2,369	66,006	30 (30–30)	3	81 (34–95)
≥150 days after full vaccination	2,129	104,174	52 (37–64)	18	73 (49–86)
Pre-Delta variant predominance					
Unvaccinated	4,137	156,626	19 (8–43)	175	N/A
Fully vaccinated	2,875	329,865	124 (95–149)	10	91 (81–96)
Delta variant predominance					
Unvaccinated	488	24,871	43 (37–69)	19	N/A
Fully vaccinated	2,352	119,218	49 (35–56)	24	66 (26–84)

Abbreviations: CI = confidence interval; IQR = interquartile range; N/A = not applicable; SMD = standardized mean difference; VE = vaccine effectiveness.

* Person-days between the date of any dose of COVID-19 vaccine and fully vaccinated status were excluded from VE models because of indeterminate immune status. Participants with SARS-CoV-2 infection during this period were also excluded; in the pre-Delta period, 47 participants were excluded, and in the Delta period, two participants were excluded. Contributing participants in vaccination categories also do not equal the total number of participants in the cohort.

† Adjusted VE was inversely weighted for probability of being vaccinated and adjusted for local virus circulation, study location, and occupation. Delta variant models were additionally adjusted for ethnicity. All Cox regression models met the proportional hazards assumption. To calculate the probability of being vaccinated for each period, boosted regression models were fit including covariates for site, sociodemographic characteristics, health information, frequency of close social contact, mask use, and local virus circulation. In the full cohort to date and the pre-Delta cohort, all covariates met balance criteria of SMD<0.2 after weighting except mask use at work (SMD = 0.227 and 0.207, respectively) but was not found to change VE estimates by ≥3% when added to the models. In the Delta predominant cohort occupation, ethnicity, influenza vaccination, and mask use at work did not meet balance criteria (SMD range = 0.206–0.288); influenza vaccination and mask use at work did not change VE estimates by ≥3%; however, occupation and ethnicity did change VE by ≥3% and were therefore included as covariates in the Cox regression model for VE.

§ Fully vaccinated was defined as ≥14 days after receipt of all recommended COVID-19 vaccine doses.

variant to 66% since the SARS-CoV-2 Delta variant became predominant at the HEROES-RECOVER cohort study sites; however, this trend should be interpreted with caution because VE might also be declining as time since vaccination increases and because of poor precision in estimates due to limited number of weeks of observation and few infections among participants. As with all observational VE studies, unmeasured and residual confounding might be present. Active surveillance through the cohort is ongoing and VE estimates will be monitored continuously. Although these interim findings suggest a moderate reduction in the effectiveness of COVID-19 vaccines in preventing infection, the sustained two thirds reduction in infection risk underscores the continued importance and benefits of COVID-19 vaccination.

Acknowledgments

Mark G. Thompson, Lauren Grant, Julie Mayo Lamberte, Young M. Yoo, Gregory Joseph, Josephine Mak, Monica Dickerson, Suxiang Tong, John Barnes, Eduardo Azziz-Baumgartner, Melissa L. Arvay, Preeta Kutty, Alicia M. Fry, Lenee Blanton, Jill Ferdinands, Anthony Fiore, Aron Hall, Adam MacNeil, L. Clifford McDonald, Mary Reynolds, Sue Reynolds, Stephanie Schrag, Nong Shang, Robert Slaughter, Matthew J. Stuckey, Natalie Thornburg, Jennifer Verani, Vic Veguilla, Rose Wang, Bao-Ping Zhu, William Brannen, Stephanie Bialek, CDC; Jefferey L. Burgess, Karen Lutrick, Shawn Beitel, Patrick Rivers, Xiaoxiao Sun, Joe K. Gerald, Janko Nikolich-Žugich, Genesis Barron, Dimaye Calvo, Esteban Cardona, Andrea Carmona, Alissa Coleman, Zoe Baccam, Emily Cooksey, Kiara Earley, Natalie Giroux, Sofia Grijalva, Allan Guidos, Adrianna Hernandez, James Hollister, Theresa Hopkins, Rezwana Islam, Krystal Jovel, Olivia Kavanagh, Jonathan Leyva, Sally Littau, Amelia Lobos, James Lopez, Veronica Lugo, Jeremy Makar, Taylor Maldonado, Enrique Marquez, Allyson Munoz, Assumpta Nsengiyunva, Joel Parker, Jonathan Perez Leyva, Alexa Roy, Saskia Smidt, Isabella Terrazas, Tahlia Thompson, Heena Timsina, Erica Vanover, Mandie White, April Yingst, Kenneth Komatsu, Elizabeth Kim, Karla Ledezma, University of Arizona, Arizona Department of Health Services; David Engelthaler, Translational Genomics Research Institute; Lauren E.W. Olsho, Danielle R. Hunt, Laura J. Edwards, Meredith G. Wesley, Meghan K. Herring, Tyler C. Morrill, Brandon P. Poe, Brian Sokol, Andrea Bronaugh, Tana Brummer, Hala Deeb, Rebecca Devlin, Sauma Doka, Tara Earl, Jini Etolue, Deanna Fleary, Jessica Flores, Chris Flygare, Isaiah Gerber, Louise Hadden, Jenna Harder, Lindsay LeClair, Nancy McGarry, Peenaz Mistry, Steve Pickett, Khaila Prather, David Pulaski, Rajbansi Raorane, Meghan Shea, John Thacker, Matthew Trombley, Pearl Zheng, Chao Zhou, Abt Associates; Kayan Dunnigan, Spencer Rose, Tnelda Zunie, Michael E. Smith, Kempapura Murthy, Nicole Calhoun, Claire Mathenge, Arundhati Rao, Manohar Mutnal, Linden Morales, Shelby Johnson, Alejandro Arroliga, Madhava Beeram, Joel Blais, Jason Ettlinger, Angela Kennedy, Natalie Settele, Rupande Patel, Elisa Priest, Jennifer Thomas, Baylor Scott & White Health; Allison L. Naleway, Holly C. Groom, Jennifer L. Kuntz, Yolanda Prado, Daniel Sapp, Mi Lee, Chris Eddy,

Matt Hornbrook, Danielle Millay, Dorothy Kurdyla, Ambrosia Bass, Kristi Bays, Kimberly Berame, Cathleen Bourdoin, Carlea Buslach, Jennifer Gluth, Kenni Graham, Tarika Holness Enedina Luis, Abreeanah Magdaleno, DeShaun Martin, Joyce Smith-McGee, Martha Perley, Sam Peterson, Aaron Piepert, Krystil Phillips, Joanna Price, Sperry Robinson, Katrina Schell, Emily Schield, Natosha Shirley, Anna Shivinsky, Britta Torgrimson-Ojerio, Brooke Wainwright, Shawn Westaway, Kaiser Permanente Northwest; Jennifer Meece, Elisha Stefanski, Lynn Ivacic, Jake Andreae, Adam Bissonnette, Krystal Boese, Michaela Braun, Cody DeHamer, Timothy Dziedzic, Joseph Eddy, Heather Edgren, Wayne Frome, Nolan Herman, Mitchell Hertel, Erin Higdon, Rosebud Johnson, Steve Kaiser, Tammy Koepel, Sarah Kohn, Taylor Kent, Thao Le, Carrie Marcis, Megan Maronde, Isaac McCready, Nidhi Mehta, Daniel Miesbauer, Anne Nikolai, Brooke Olson, Lisa Ott, Cory Pike, Nicole Price, Christopher Reardon, Logan Schafer, Rachel Schoone, Jaclyn Schneider, Tapan Sharma, Melissa Strupp, Janay Walters, Alyssa Weber, Reynor Wilhorn, Ryan Wright, Benjamin Zimmerman, Marshfield Clinic Research Laboratory; Angela Hunt, Jessica Lundgreen, Karley Respet, Jennifer Viergutz, Daniel Stafki, St. Luke's Regional Health Care System; Alberto J. Caban-Martinez, Natasha Schaefer-Solle, Paola Louzado Feliciano, Carlos Silvera, Karla Montes, Cynthia Beaver, Katerina Santiago, University of Miami; Sarang K. Yoon, Kurt Hegmann, Andrew L. Phillips, Rachel T. Brown, Camie Schaefer, Arlyne Arteaga, Matthew Bruner, Daniel Dawson, Emilee Eden, Jenna Praggastis, Joseph Stanford, Jeanmarie Mayer, Marcus Stucki, Riley Campbell, Kathy Tran, Madeleine Smith, Braydon Black, Madison Tallman, Chapman Cox, Derrick Wong, Michael Langston, Adriele Fugal, Fiona Tsang, Maya Wheeler, Gretchen Maughan, Taryn Hunt-Smith, Nikki Gallacher, Anika DSouza, Trevor Stubbs, Iman Ibrahim, Ryder Jordin, University of Utah; Marilyn J. Odean, Whiteside Institute for Clinical Research; Allen Bateman, Erik Reisdorf, Kyley Guenther, Erika Hanson, Wisconsin State Laboratory of Hygiene; the HEROES-RECOVER participants.

Corresponding author: Ashley Fowlkes, afowlkes@cdc.gov

[1]CDC COVID-19 Response Team; [2]Baylor Scott and White Health, Texas A&M University College of Medicine, Temple, Texas; [3]Abt Associates, Inc., Rockville, Maryland; [4]University of Utah, Salt Lake City, Utah; [5]St. Luke's Regional Health Care System, Duluth, Minnesota; [6]Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Matthew S. Thiese reports grants and personal fees from Reed Group and the American College of Occupational and Environmental Medicine, outside the submitted work. No other potential conflicts of interest were disclosed.

References

1. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med 2021;385:320–9. PMID:34192428 https://doi.org/10.1056/NEJMoa2107058
2. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—eight U.S. locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495–500. PMID:33793460 https://doi.org/10.15585/mmwr.mm7013e3
3. Herlihy R, Bamberg W, Burakoff A, et al. Rapid increase in circulation of the SARS-CoV-2 B.1.617.2 (Delta) variant—Mesa County, Colorado, April–June 2021. MMWR Morb Mortal Wkly Rep 2021;70:1084–7. PMID:34383734 https://doi.org/10.15585/mmwr.mm7032e2
4. Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings—Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep 2021;70:1059–62. PMID:34351882 https://doi.org/10.15585/mmwr.mm7031e2
5. Lutrick K, Ellingson KD, Baccam Z, et al. COVID-19 infection, reinfection, and vaccine effectiveness in a prospective cohort of Arizona frontline/essential workers: the AZ HEROES research protocol. JMIR Res Protoc 2021. Epub May 26, 2021. PMID:34057904 https://doi.org/10.2196/28925
6. US Department of Health and Human Services. HHS protect public data hub. Washington, DC: US Department of Health and Human Services; 2021. Accessed August 16, 2021. https://protect-public.hhs.gov/

Exhibit E

Effectiveness of COVID-19 vaccines against Omicron or Delta infection

Sarah A. Buchan, PhD[1,2,3,4], Hannah Chung, MPH[2], Kevin A. Brown, PhD[1,2,3], Peter C. Austin, PhD[2,5], Deshayne B. Fell, PhD[6,7], Jonathan B. Gubbay, MBBS[1,8], Sharifa Nasreen, PhD[2,3], Kevin L. Schwartz, MD[1,2,3], Maria E. Sundaram PhD[9], Mina Tadrous, PhD[2,10,11], Kumanan Wilson, MD[12,13], Sarah E. Wilson, MD[1,2,3,4], Jeffrey C. Kwong, MD[1,2,3,4,14,15] on behalf of the Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Investigators

[1] Public Health Ontario, Toronto, ON

[2] ICES, Toronto, ON

[3] Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[4] Centre for Vaccine Preventable Diseases, University of Toronto, Toronto, ON

[5] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON

[6] School of Epidemiology and Public Health, University of Ottawa, ON

[7] Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON

[8] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON

[9] Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, Marshfield, WI, USA

[10] Women's College Hospital, Toronto, ON

[11] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON

[12] Department of Medicine, University of Ottawa, Ottawa, ON

[13] Bruyere and Ottawa Hospital Research Institutes, Ottawa, ON

[14] Department of Family and Community Medicine, University of Toronto, Toronto, ON

[15] University Health Network, Toronto, ON

*Corresponding author:

Jeff Kwong

Senior Scientist, ICES

G1 06, 2075 Bayview Avenue, Toronto, Ontario, Canada, M4N 3M5

jeff.kwong@utoronto.ca

Phone: (416) 480-4055 x1-7665

Fax: (416) 480-6048

Abstract word count: 241

Manuscript word count: 2,701

Tables/Figures: 3

References: 32

ABSTRACT

Background

The incidence of SARS-CoV-2 infection, including among those who have received 2 doses of COVID-19 vaccines, has increased substantially since Omicron was first identified in the province of Ontario, Canada.

Methods

Applying the test-negative design to linked provincial data, we estimated vaccine effectiveness against infection (irrespective of symptoms or severity) caused by Omicron or Delta between November 22 and December 19, 2021. We included individuals who had received at least 2 COVID-19 vaccine doses (with at least 1 mRNA vaccine dose for the primary series) and used multivariable logistic regression to estimate the effectiveness of two or three doses by time since the latest dose.

Results

We included 3,442 Omicron-positive cases, 9,201 Delta-positive cases, and 471,545 test-negative controls. After 2 doses of COVID-19 vaccine, vaccine effectiveness against Delta infection declined steadily over time but recovered to 93% (95%CI, 92-94%) ≥7 days after receiving an mRNA vaccine for the third dose. In contrast, receipt of 2 doses of COVID-19 vaccines was not protective against Omicron. Vaccine effectiveness against Omicron was 37% (95%CI, 19-50%) ≥7 days after receiving an mRNA vaccine for the third dose.

Conclusions

Two doses of COVID-19 vaccines are unlikely to protect against infection by Omicron. A third dose provides some protection in the immediate term, but substantially less than against Delta. Our results may be confounded by behaviours that we were unable to account for in our analyses. Further research is needed to examine protection against severe outcomes.

INTRODUCTION

The World Health Organization declared Omicron a Variant of Concern on November 26, 2021 due to its highly transmissible nature and risk of immune evasion.[1] In Ontario, Canada, the first detected case of Omicron was identified on November 22, 2021; within weeks, Omicron accounted for the majority of new cases. Despite very high 2-dose COVID-19 vaccine coverage (88% among those aged ≥12 years by mid-December),[2] the rate of cases among fully vaccinated individuals increased substantially during this period.[3]

While reduced neutralizing antibodies against Omicron following second and third doses of mRNA vaccines has been established,[4-9] real-world data evaluating vaccine performance against Omicron infection are more limited,[10-12] particularly in a North American context. The objective of this study was to estimate vaccine effectiveness (VE) against infection caused by Omicron or Delta in Ontario.

METHODS

Study population, setting, and design

We used the test-negative design and linked provincial data to estimate VE. We included all individuals aged ≥18 years with provincial health insurance who had a reverse transcription real-time polymerase chain reaction (PCR) test for SARS-CoV-2 between November 22 and December 19, 2021.

We excluded: long-term care residents; individuals who had received only 1 dose of COVID-19 vaccine or who had received their second dose <7 days prior to being tested; individuals who had received 2 doses of ChAdOx1 (AstraZeneca Vaxzevria, COVISHIELD) because VE for that schedule is known to be lower; those who had received non-Health Canada authorized vaccine(s); and those who received the Janssen (Johnson & Johnson) vaccine (which, while approved for use in Canada, was largely unavailable and very rarely used).

Data sources

We linked provincial SARS-CoV-2 laboratory testing, reportable disease, COVID-19 vaccination, and health administrative databases using unique encoded identifiers and analyzed them at ICES, a not-for-profit provincial research institute (www.ices.on.ca).

Outcomes

We identified individuals with confirmed SARS-CoV-2 infections using provincial reportable disease data. We included confirmed COVID-19 cases irrespective of symptoms or severity. The specimen

collection date was used as the index date. For individuals who tested negative for SARS-CoV-2 during the study period and were considered as controls, we randomly selected one negative test to use as the index date. To ensure that negative tests were not associated with recent illness, we excluded controls who tested positive for SARS-CoV-2 within the past 90 days.

Positive specimens identified through whole genome sequencing as B.1.1.529 lineage or found to have S-gene Target Failure (SGTF; a proxy measure for Omicron resulting from the amino acid 69-70 spike deletion that does not occur with Delta) were considered Omicron infections, and specimens sequenced as B.1.617 lineage, found to be negative for SGTF, or collected prior to December 3 (when the prevalence of Omicron was <5%) and had no SGTF information, were considered Delta infections. As of December 6, 2021, all specimens with a positive PCR result were re-tested using Thermofisher Taqpath™ COVID-19 PCR to identify SGTF. Prior to this date, SGTF specimens were only identified if the particular testing laboratory used the Taqpath™ platform. Between December 6 and 20, all SGTF-positive specimens with cycle threshold (Ct) values ≤30 also underwent whole genome sequencing (WGS). In Ontario, the estimated sensitivity of SGTF relative to WGS for detecting Omicron among samples with Ct ≤30 was 99.5% and the specificity was 99.8%.[13]

COVID-19 vaccination

To date, Ontario has primarily used 3 products (BNT162b2 [Pfizer-BioNTech Comirnaty], mRNA-1273 [Moderna Spikevax], and ChAdOx1) in its COVID-19 vaccination program. Due to fluctuating vaccine supplies, both varying dosing intervals and mixed vaccine schedules were employed. Using a centralized province-wide vaccine registry to identify receipt of COVID-19 vaccines, we classified individuals depending on whether they had received 2 or 3 doses of vaccine and the timing of these doses relative to the index date. We considered the following vaccine schedules for the primary 2-dose series: receipt of at least 1 mRNA vaccine (since a mixed schedule consisting of ChAdOx1 and an mRNA vaccine has previously been demonstrated to have similar VE as 2 mRNA vaccines),[14] receipt of any combination of 2 mRNA vaccines, and receipt of 2 doses of BNT162b2. For the third dose, we considered receipt of any mRNA vaccine and also compared receipt of BNT162b2 with mRNA-1273. All comparisons used those who had not yet received any doses (i.e., “unvaccinated”) by the testing date as the reference group.

Third dose eligibility in Ontario began in August 2021 and expanded gradually.[15] Initially, only moderately or severely immunocompromised individuals were eligible to receive a third dose as part of an extended primary series. Shortly thereafter, third doses (i.e., ‘boosters’) were provided to residents of higher-risk congregate settings for older adults (e.g., long-term care homes, high-risk retirement

homes). In early October, older adults living in other congregate care settings, including all remaining retirement homes, became eligible. All individuals aged ≥70 years and healthcare workers became eligible on November 6, followed by individuals aged ≥50 years on December 13 and individuals aged ≥18 years on December 18. The standard interval for third dose eligibility was generally ≥168 days following the second dose but was shortened to ≥84 days on December 15.

Covariates

From various databases, we obtained information on each individual's age, sex, public health unit region of residence, number of SARS-CoV-2 PCR tests during the 3 months prior to December 14, 2020 (as a proxy for healthcare worker status based on the start date of the provincial COVID-19 vaccine program), past SARS-CoV-2 infection >90 days prior to testing date, comorbidities associated with increased risk of severe COVID-19, influenza vaccination status during the 2019/2020 and/or 2020/2021 influenza seasons (as a proxy for health behaviours), and neighbourhood-level information on median household income, proportion of the working population employed as non-health essential workers, mean number of persons per dwelling, and proportion of the population who self-identify as a visible minority. These databases and definitions have been fully described elsewhere.[16]

Statistical analysis

For both Omicron and Delta infections, we calculated means (continuous variables) and frequencies (categorical variables) and compared test-positive cases and test-negative controls using standardized differences.

We used multivariable logistic regression to estimate odds ratios comparing the odds of vaccination in each "time since latest dose" interval among cases with the odds among controls, while adjusting for all listed covariates and a categorical variable for week of test. VE was calculated using the formula VE=(1-OR)x100%. For both Omicron and Delta infections, we estimated VE by vaccine schedule and time since latest dose.

All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC). All tests were two-sided and used $p<0.05$ as the level of statistical significance.

RESULTS

Between November 22 and December 19, 2021, we included 3,442 Omicron-positive cases, 9,201 Delta-positive cases, and 471,545 test-negative controls. Compared to controls, Omicron cases were: substantially younger (mean age 34.9 years vs. 45.0 years); more likely to be male; less likely to have

any comorbidities; less likely to have had multiple prior SARS-CoV-2 tests; less likely to have received an influenza vaccine during the previous 2 influenza seasons; more likely to have occurred during the latter half of the study period; less likely to have previously tested positive for SARS-CoV-2; more likely to have received 2 doses of COVID-19 vaccines; and less likely to have received a third dose (Table 1).

In contrast, Delta cases were more similar to controls than Omicron cases in some respects (e.g., age, comorbidities) but were more different in others, such as being more likely to have occurred during the initial half of the study period, far more likely to be unvaccinated (33.1% vs. 7.5%), and less likely to have received 2 or 3 doses.

After 2 doses of COVID-19 vaccines (with at least 1 mRNA vaccine), VE against Delta declined steadily over time from 84% (95%CI, 81-86%) 7-59 days after the second dose to 71% (95%CI, 66-75%) ≥240 days after the second dose, but recovered to 93% (95%CI, 92-94%) ≥7 days after receiving an mRNA vaccine for the third dose (Table 2; Figure 1). In contrast, receipt of 2 doses of COVID-19 vaccines was not protective against Omicron infection at any point in time, and VE was –38% (95%CI, –61%, –18%) 120-179 days and –42% (95%CI, –69%, –19%) 180-239 days after the second dose. VE against Omicron was 37% (95%CI, 19-50%) ≥7 days after receiving an mRNA vaccine for the third dose.

Findings were consistent for any combination of 2 mRNA vaccines and 2 doses of BNT162b2 for the primary series (Table S1, Figure S1).

DISCUSSION

Our results demonstrate that the effectiveness of 2 doses of COVID-19 vaccines against infection (irrespective of symptoms or severity) is substantially lower for Omicron than Delta, and that VE against Omicron infection was only 37% ≥7 days following a third dose. We also observed negative VE against Omicron among those who had received 2 doses compared to unvaccinated individuals.

Early estimates of VE against the Omicron variant are available from several countries, including England, Scotland, Denmark, and South Africa. In a test-negative study conducted in England, Andrews et al. found substantial waning of VE after 2 doses, and lower VE against symptomatic infection from Omicron than Delta at each time point following 2 or 3 doses.[10 17] While lower than for Delta, VE against Omicron was restored to ~70% in the 4 weeks following a third dose and subsequently waned. Similar to those findings, our results show a marked reduction in 2-dose effectiveness against Omicron infection relative to Delta, followed by increased effectiveness after a third dose. While the pattern of our results were similar, our absolute estimates were lower. Our results

align more closely with recent Danish data, where VE was estimated for both BNT162b2 and mRNA-1273 vaccines between November 20 and December 12, 2021.[12] In both Ontario and Denmark, VE was estimated against any infection; these estimates are expected to be lower than against symptomatic infection. In the Danish study, there was no significant protection against Omicron infection beyond 31 days after the second dose of BNT162b2, with significant negative VE estimates 91-150 days after the second dose. We also observed a pattern of non-existent, or even negative VE in Ontario. However, VE in Denmark (available for BNT162b2 only) recovered to 55% in the first 30 days following a third dose. The Danish estimates are also aligned with other study results from England,[11] where an estimated VE of 0-20% against symptomatic infection was observed for those with 2 doses of BNT162b2 and 55-80% for those with 3 doses, and from Scotland,[18] where relative VE against Omicron following a third dose was estimated at 56-57% in the 2 weeks following a third dose compared to those who had received 2 vaccine doses ≥25 weeks before the symptom onset date. Finally, a study from South Africa estimated VE against infection at 33% in the Omicron period compared to 77% in the pre-Omicron period.[19]

Direct comparisons to other jurisdictions are challenging[20] due to differences in study methodology, outcome definitions (i.e., symptomatic infection vs. any infection), vaccination policies (i.e., homologous vs. heterologous vaccine schedules, third dose eligibility criteria, product-specific policies), population age structures, and public health measures that were in place during the study period (e.g., vaccine certificates, mask mandates[21]). Despite this, the general trends across the studies are similar, demonstrating substantially lower VE against Omicron infection than for previous SARS-CoV-2 variants.

The behaviour of individuals who are vaccinated, and the policies that apply to this group, may differ from those who are unvaccinated such that “vaccinated” status could be associated with an increased risk of exposure. In Ontario, a vaccine certificate system was introduced in the fall of 2021, such that only individuals who have received 2 doses of vaccine are permitted to travel by air and rail, and to enter restaurants, bars, gyms, and large cultural and sporting events. Younger adults may be more likely to frequent such venues and have more social contacts[22] (and Omicron cases in our study were younger). As such, the exposure risk of vaccinated individuals may be higher than unvaccinated individuals since vaccination is a requirement to participate in these social activities. This may explain the negative VE following 2 doses observed for Omicron during this early study period. In earlier work, we noted negative VE in the first week following the second dose against previous variants, in keeping with the hypothesis that a mistaken belief in immediate protection post-vaccination may lead to premature behaviour change. However, other hypotheses should also be considered, including the

possibility that antigenic imprinting could impact the immune response to Omicron.[23] Ontario has experienced a lower cumulative incidence of reported infections and has attained higher vaccine coverage, and thus has a potentially dissimilar distribution of infection-induced versus vaccine-induced immunity, than other countries that have estimated VE against Omicron to date.[24]

In addition to the potential that behavioural patterns differ by age, the characteristics of individuals who received specific products may differ due to a preferential recommendation in Ontario of BNT162b2 for young adults.[25 26] This may be another contributing factor in observed differences in VE across products (i.e., higher VE for mRNA-1273 than BNT162b2) in other studies.[17 27 28]

Although prior studies have demonstrated reduced neutralizing antibodies against Omicron relative to other variants following receipt of 2 mRNA vaccines[4-7 9] (but with potent neutralization following a third dose[29 30]), CD8+ cytotoxic T cells are less impacted by mutations in the Omicron variant and are likely to continue to provide protection against severe disease.[30 31] To date, little real-world data on protection against hospitalization are available. In South Africa, effectiveness against hospitalization was reduced from 93% in the pre-Omicron period to 70% in the Omicron period.[19 32] In England, VE against hospitalization due to Omicron also appears to be better maintained relative to infection with Omicron.[11] Further data on effectiveness of 2 or 3 doses against severe outcomes are needed.

Our analysis has several limitations. First, we were unable to differentiate individuals who received a third dose as part of an extended primary series (i.e., severely or moderately immunocompromised individuals) as well as those who were eligible for a third dose earlier (e.g., residents of retirement homes). As such, the proportion of our sample with a third dose may reflect these highly vulnerable populations, and thus VE may be lower than for the general population due to underlying comorbidities, for example. Second, due to sample size constraints, we were unable to provide age-specific VE estimates. Third, we were unable to estimate effectiveness against severe outcomes, due to the lag between infection and hospitalization or death. Fourth, there may be residual confounding that was not accounted for in our analysis. This includes an inability to control for previous undocumented infections, which may be differential by vaccination status, as well as confounding due to behavioural patterns. For example, if vaccinated individuals have more exposure to SARS-CoV-2, our VE estimates are likely underestimated.[21] Last, changes in testing patterns, including increased use of rapid antigen tests (which are not captured in our data) and decreased PCR testing availability, may have impacted our estimates, but the direction of any resulting bias is uncertain.

Our findings have potentially important implications for proof of vaccination requirements. If the goal of these policies is to protect against infection then individuals who have received 2 doses of

mRNA vaccines may no longer be considered fully vaccinated. However, if the primary goal of these policies is to protect against severe illness and impact on the health system, further data will be needed to determine the number of doses required to provide adequate protection against severe outcomes caused by Omicron. Our work adds to an emerging body of research that suggests that immunization status cannot be simply dichotomized, and that protection is instead based on a variety of factors such as type of vaccine received, age of recipient, time since latest dose, and circulating variant.

Conclusions

Two doses of COVID-19 vaccines are unlikely to protect against Omicron infection. While VE against Omicron infection is substantially lower than against Delta infection, a third dose of mRNA vaccine affords some level of protection against Omicron infection in the immediate term. However, the duration of this protection and effectiveness against severe disease are uncertain. Additional tools beyond the currently available vaccines, such as public health measures, antivirals, and updated vaccines, are likely needed to protect against Omicron infection.

Ethics approval

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

Data availability

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca).

Code availability

The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Acknowledgments

We would like to acknowledge Public Health Ontario for access to vaccination data from COVaxON, case-level data from CCM and COVID-19 laboratory data, as well as assistance with data interpretation. We also thank the staff of Ontario's public health units who are responsible for COVID-19 case and contact management and data collection within CCM. We thank IQVIA Solutions Canada Inc. for use of their Drug Information Database. The authors are grateful to the Ontario residents without whom this research would be impossible.

Author contributions

S.A.B, H.C., and J.C.K. designed the study. H.C. obtained the data and conducted all analyses (data set and variable creation and statistical modelling). S.A.B. and J.C.K. drafted the manuscript. All authors contributed to the analysis plan, interpreted the results, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Competing interests

K.W. is CEO of CANImmunize and serves on the data safety board for the Medicago COVID-19 vaccine trial. The other authors declare no conflicts of interest.

Funding and disclaimers

This work was supported by the Canadian Immunization Research Network (CIRN) through a grant from the Public Health Agency of Canada and the Canadian Institutes of Health Research (CNF 151944). This project was also supported by funding from the Public Health Agency of Canada, through the Vaccine Surveillance Reference Group and the COVID-19 Immunity Task Force. This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH). J.C.K. is supported by Clinician-Scientist Award from the University of Toronto Department of Family and Community Medicine. P.C.A. is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation.

This work was supported by Public Health Ontario. This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This study was supported by the Ontario Health Data Platform (OHDP), a Province of Ontario initiative to support Ontario's ongoing response to COVID-19 and its related impacts. The study sponsors did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI) and by Cancer Care Ontario (CCO). However, the analyses, conclusions, opinions and statements expressed herein are solely those of the authors, and do not reflect those of the funding or data sources; no endorsement by ICES, MOH, MLTC, OHDP, its partners, the Province of Ontario, CIHI or CCO is intended or should be inferred.

References

1. World Health Organization (WHO). Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern [Internet] Geneva: WHO; 2021 [Available from: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern.
2. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 Vaccine Uptake and Program Impact in Ontario: December 14, 2020 to December 19, 2021 Toronto, ON: Queen's Printer for Ontario2021 [Available from: https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?sc_lang=en accessed 30 December 2021.
3. Government of Ontario. COVID-19 vaccinations data: Queen's Printer for Ontario; [Available from: https://covid-19.ontario.ca/data accessed December 25 2021.
4. Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. *N Engl J Med* 2021 doi: 10.1056/NEJMc2119358
5. Cele S, Jackson L, Khoury DS, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. *medRxiv* 2021:2021.12.08.21267417. doi: 10.1101/2021.12.08.21267417
6. Rössler A, Riepler L, Bante D, et al. SARS-CoV-2 B.1.1.529 variant (Omicron) evades neutralization by sera from vaccinated and convalescent individuals. *medRxiv* 2021:2021.12.08.21267491. doi: 10.1101/2021.12.08.21267491
7. Wilhelm A, Widera M, Grikscheit K, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. *medRxiv* 2021:2021.12.07.21267432. doi: 10.1101/2021.12.07.21267432
8. Dejnirattisai W, Shaw RH, Supasa P, et al. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. *Lancet* 2021:DOI: https://doi.org/10.1016/S0140-6736(21)02844-0. doi: 10.1016/S0140-6736(21)02844-0
9. Sheward DJ, Kim C, Pankow A, et al. Quantification of the neutralization resistance of the Omicron Variant of Concern. *Preliminary Report - Early release, subject to modification* 2021
10. Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. *medRxiv* 2021:2021.12.14.21267615. doi: 10.1101/2021.12.14.21267615
11. Ferguson N, Ghani A, Cori A, et al. Report 49: Growth, population distribution and immune escape of Omicron in England. *Imperial College London (16-12-2021), doi: https://doiorg/1025561/93038* 2021
12. Hansen CH, Schelde AB, Moustsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study. *medRxiv* 2021:2021.12.20.21267966. doi: 10.1101/2021.12.20.21267966
13. Ontario Agency for Health Protection and Promotion (Public Health Ontario). SARS-CoV-2 (COVID-19 Virus) Variant of Concern (VoC) Screening and Genomic Sequencing for Surveillance. SARS-COV-2 VoC S-Gene Deletion Screen by Real-Time PCR 2021 [Available from: https://www.publichealthontario.ca/en/laboratory-services/test-information-index/covid-19-voc accessed 28 December 2021.
14. Skowronski DM, Setayeshgar S, Febriani Y, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. *medRxiv* 2021:2021.10.26.21265397. doi: 10.1101/2021.10.26.21265397
15. Government of Ontario. Getting the COVID-19 vaccine: Queen's Printer for Ontario; [Available from: https://covid-19.ontario.ca/getting-covid-19-vaccine#which-vaccine-you-can-get accessed December 23 2021.

16. Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. *BMJ* 2021;374:n1943. doi: 10.1136/bmj.n1943
17. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 33 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf accessed 22 December 2021.
18. Sheikh A, Kerr S, Woolhouse M, et al. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. Preprint 2021 [Available from: https://www.pure.ed.ac.uk/ws/portalfiles/portal/245818096/Severity_of_Omicron_variant_of_concern_and_vaccine_effectiveness_against_symptomatic_disease.pdf.
19. Discovery Health. Discovery Health, South Africa's largest private health insurance administrator, releases at-scale, real-world analysis of Omicron outbreak based on 211 000 COVID-19 test results in South Africa, including collaboration with the South Africa 2021 [Available from: https://www.discovery.co.za/corporate/news-room#/documents/presentation-deck-omicron-insights-final-14-december-2021-at-08h00-dot-pdf-417949 accessed 22 December 2021.
20. Lipsitch M, Krammer F, Regev-Yochay G, et al. SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact. *Nat Rev Immunol* 2022;22(1):57-65. doi: 10.1038/s41577-021-00662-4
21. Matytsin A. The Mask-Wearing Bias In The Estimates Of Vaccine Efficacy. *medRxiv* 2021:2021.10.19.21265093. doi: 10.1101/2021.10.19.21265093
22. Brankston G, Merkley E, Fisman DN, et al. Quantifying contact patterns in response to COVID-19 public health measures in Canada. *BMC Public Health* 2021;21(1):2040-40. doi: 10.1186/s12889-021-12080-1
23. Monto AS, Malosh RE, Petrie JG, et al. The Doctrine of Original Antigenic Sin: Separating Good From Evil. *J Infect Dis* 2017;215(12):1782-88. doi: 10.1093/infdis/jix173
24. Our World in Data. Coronavirus (COVID-19) Cases [Available from: https://ourworldindata.org/covid-cases accessed 30 December 2021.
25. Buchan SA, Seo CY, Johnson C, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. *medRxiv* 2021:2021.12.02.21267156. doi: 10.1101/2021.12.02.21267156
26. Ontario Ministry of Health. COVID-19 Vaccine Information Sheet (age 12+) 2021 [Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/COVID-19_vaccine_info_sheet.pdf accessed 22 December 2021.
27. Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. *N Engl J Med* 2021 doi: 10.1056/NEJMoa2115463
28. Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. *MMWR Morb Mortal Wkly Rep* 2021;70(38):1337-43. doi: 10.15585/mmwr.mm7038e1
29. Garcia-Beltran WF, St. Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *medRxiv* 2021:2021.12.14.21267755. doi: 10.1101/2021.12.14.21267755
30. Pfizer Press Release. Pfizer and BioNTech Provide Update on Omicron Variant 2021 [cited 2021 22 December]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant.

31. Redd AD, Nardin A, Kared H, et al. Minimal cross-over between mutations associated with Omicron variant of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals. *bioRxiv* 2021:2021.12.06.471446. doi: 10.1101/2021.12.06.471446
32. Collie S, Champion J, Moultrie H, et al. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. *N Engl J Med* 2021 doi: 10.1056/NEJMc2119270

Table 1. Characteristics of study subjects tested for SARS-CoV-2 between 22 November and 19 December 2021 in Ontario, Canada

	SARS-CoV-2 negative, n (%)[a]	Omicron, n (%)[a]	SD[b]	Delta, n (%)[a]	SD[b]
Total	471,545	3,442	N/A	9,201	N/A
Subject characteristics					
Age (years), mean (standard deviation)	45.04 ± 17.66	34.87 ± 13.71	0.64	43.76 ± 16.30	0.08
Age group (years)					
18–29	104,897 (22.2%)	1,528 (44.4%)	0.48	2,002 (21.8%)	0.01
30–39	106,181 (22.5%)	742 (21.6%)	0.02	2,215 (24.1%)	0.04
40–49	83,328 (17.7%)	638 (18.5%)	0.02	1,901 (20.7%)	0.08
50–59	74,452 (15.8%)	351 (10.2%)	0.17	1,396 (15.2%)	0.02
60–69	52,441 (11.1%)	117 (3.4%)	0.3	941 (10.2%)	0.03
70–79	30,559 (6.5%)	49 (1.4%)	0.26	528 (5.7%)	0.03
≥80	19,687 (4.2%)	17 (0.5%)	0.25	218 (2.4%)	0.10
Male sex	202,843 (43.0%)	1,695 (49.2%)	0.13	4,529 (49.2%)	0.12
Any comorbidity[c]	215,267 (45.7%)	1,220 (35.4%)	0.21	3,986 (43.3%)	0.05
Number of SARS-CoV-2 tests within 3 months prior to 14 Dec 2020					
0	351,505 (74.5%)	2,600 (75.5%)	0.02	7,519 (81.7%)	0.17
1	80,508 (17.1%)	651 (18.9%)	0.05	1,248 (13.6%)	0.10
≥2	39,532 (8.4%)	191 (5.5%)	0.11	434 (4.7%)	0.15
Receipt of 2019-2020 and/or 2020-2021 influenza vaccination	162,615 (34.5%)	890 (25.9%)	0.19	2,142 (23.3%)	0.25
Public health unit region[d]					
Central East	31,437 (6.7%)	122 (3.5%)	0.14	875 (9.5%)	0.1
Central West	86,882 (18.4%)	780 (22.7%)	0.10	1,701 (18.5%)	0
Durham	20,988 (4.5%)	233 (6.8%)	0.10	304 (3.3%)	0.06
Eastern	38,635 (8.2%)	376 (10.9%)	0.09	713 (7.7%)	0.02
North	31,375 (6.7%)	35 (1.0%)	0.30	847 (9.2%)	0.09
Ottawa	32,836 (7.0%)	309 (9.0%)	0.07	475 (5.2%)	0.08
Peel	42,643 (9.0%)	442 (12.8%)	0.12	873 (9.5%)	0.02
South West	57,132 (12.1%)	122 (3.5%)	0.32	1,537 (16.7%)	0.13
Toronto	90,349 (19.2%)	746 (21.7%)	0.06	1,304 (14.2%)	0.13
York	37,420 (7.9%)	255 (7.4%)	0.02	532 (5.8%)	0.09
Household income quintile[d, e]					
1 (lowest)	82,944 (17.6%)	377 (11.0%)	0.19	1,811 (19.7%)	0.05
2	86,939 (18.4%)	465 (13.5%)	0.13	1,702 (18.5%)	0
3	92,991 (19.7%)	653 (19.0%)	0.02	1,853 (20.1%)	0.01
4	99,462 (21.1%)	771 (22.4%)	0.03	1,939 (21.1%)	0
5 (highest)	107,161 (22.7%)	1,153 (33.5%)	0.24	1,846 (20.1%)	0.06
Essential workers quintile[d, f]					
1 (0%–32.5%)	111,693 (23.7%)	1,201 (34.9%)	0.25	1,605 (17.4%)	0.15
2 (32.5%–42.3%)	107,392 (22.8%)	943 (27.4%)	0.11	1,980 (21.5%)	0.03
3 (42.3%–49.8%)	92,534 (19.6%)	584 (17.0%)	0.07	1,868 (20.3%)	0.02
4 (50.0%–57.5%)	84,326 (17.9%)	416 (12.1%)	0.16	1,816 (19.7%)	0.05
5 (57.5%–100%)	72,486 (15.4%)	272 (7.9%)	0.23	1,834 (19.9%)	0.12
Persons per dwelling quintile[d, g]					
1 (0–2.1)	91,000 (19.3%)	522 (15.2%)	0.11	1,665 (18.1%)	0.03
2 (2.2–2.4)	81,998 (17.4%)	423 (12.3%)	0.14	1,650 (17.9%)	0.01
3 (2.5–2.6)	66,496 (14.1%)	453 (13.2%)	0.03	1,389 (15.1%)	0.03
4 (2.7–3.0)	112,978 (24.0%)	912 (26.5%)	0.06	2,216 (24.1%)	0
5 (3.1–5.7)	115,770 (24.6%)	1,102 (32.0%)	0.17	2,172 (23.6%)	0.02
Self-identified visible minority quintile[d, h]					
1 (0.0%–2.2%)	75,821 (16.1%)	310 (9.0%)	0.21	1,742 (18.9%)	0.08
2 (2.2%–7.5%)	83,649 (17.7%)	514 (14.9%)	0.08	1,889 (20.5%)	0.07
3 (7.5%–18.7%)	92,075 (19.5%)	805 (23.4%)	0.09	1,832 (19.9%)	0.01

	SARS-CoV-2 negative, n (%)[a]	Omicron, n (%)[a]	SD[b]	Delta, n (%)[a]	SD[b]
4 (18.7%–43.5%)	105,666 (22.4%)	946 (27.5%)	0.12	1,867 (20.3%)	0.05
5 (43.5%–100%)	111,237 (23.6%)	841 (24.4%)	0.02	1,780 (19.3%)	0.10
Week of test					
22 November to 28 November 2021	98,419 (20.9%)	12 (0.3%)	0.71	3,359 (36.5%)	0.35
29 November to 5 December 2021	111,195 (23.6%)	55 (1.6%)	0.70	3,237 (35.2%)	0.26
6 December to 12 December 2021	126,583 (26.8%)	1,123 (32.6%)	0.13	1,530 (16.6%)	0.25
13 December to 19 December 2021	135,348 (28.7%)	2,252 (65.4%)	0.79	1,075 (11.7%)	0.43
Prior positive SARS-CoV-2 test	20,279 (4.3%)	33 (1.0%)	0.21	24 (0.3%)	0.27
COVID-19 vaccine characteristics					
Unvaccinated	35,264 (7.5%)	176 (5.1%)	0.10	3,046 (33.1%)	0.67
Received 2-dose primary series only (with at least 1 mRNA vaccine)	389,573 (82.6%)	3,102 (90.1%)	0.22	5,946 (64.6%)	0.42
Received BNT162b2 for third dose	38,730 (8.2%)	148 (4.3%)	0.16	180 (2.0%)	0.29
Received mRNA-1273 for third dose	7,978 (1.7%)	16 (0.5%)	0.12	29 (0.3%)	0.14
Time since second dose					
7-59 days	14,288 (3.0%)	63 (1.8%)	0.08	204 (2.2%)	0.05
60-119 days	34,741 (7.4%)	214 (6.2%)	0.05	562 (6.1%)	0.05
120-179 days	282,977 (60.0%)	2,257 (65.6%)	0.12	4,342 (47.2%)	0.26
180-239 days	47,282 (10.0%)	522 (15.2%)	0.16	635 (6.9%)	0.11
≥240 days	10,285 (2.2%)	46 (1.3%)	0.06	203 (2.2%)	0
Time since third dose					
No third dose (i.e., only 2 doses)	389,573 (82.6%)	3,102 (90.1%)	0.22	5,946 (64.6%)	0.42
0-6 days	10,208 (2.2%)	50 (1.5%)	0.05	71 (0.8%)	0.12
7-59 days	32,528 (6.9%)	108 (3.1%)	0.17	117 (1.3%)	0.29
≥60 days	3,972 (0.8%)	6 (0.2%)	0.09	21 (0.2%)	0.08

[a]Proportion reported, unless stated otherwise.

[b]SD=standardized difference. Standardized differences of >0.10 are considered clinically relevant. Comparison of Omicron-positive cases with SARS-CoV-2-negative controls, and Delta-positive cases with SARS-CoV-2-negative controls.

[c]Comorbidities include chronic respiratory diseases, chronic heart diseases, hypertension, diabetes, immunocompromising conditions due to underlying diseases or therapy, autoimmune diseases, chronic kidney disease, advanced liver disease, dementia/frailty and history of stroke or transient ischemic attack.

[d]The sum of counts does not equal the column total because of individuals with missing information (<1.0%) for this characteristic.

[e]Household income quintile has variable cut-off values in each city/Census area to account for cost of living. A dissemination area (DA) being in quintile 1 means it is among the lowest 20% of DAs in its city by income.

[f]Percentage of people in the area working in the following occupations: sales and service occupations; trades, transport and equipment operators and related occupations; natural resources, agriculture, and related production occupations; and occupations in manufacturing and utilities. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

[g]Range of persons per dwelling.

[h]Percentage of people in the area who self-identified as a visible minority. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

Table 2. Vaccine effectiveness against infection by Omicron or Delta among adults aged ≥18 years by time since latest dose

Doses	Vaccine products	Days since latest dose	SARS-CoV-2 negative controls, n	Omicron-positive cases, n	Vaccine effectiveness against Omicron (95% CI)	Delta-positive cases, n	Vaccine effectiveness against Delta (95% CI)
First 2 doses	≥1 mRNA vaccine	7-59	14,288	63	6 (-25, 30)	204	84 (81, 86)
		60-119	34,741	214	-13 (-38, 8)	562	81 (79, 82)
		120-179	282,977	2,257	-38 (-61, -18)	4,342	80 (79, 81)
		180-239	47,282	522	-42 (-69, -19)	635	74 (72, 76)
		≥240	10,285	46	-16 (-62, 17)	203	71 (66, 75)
Third dose	Any mRNA vaccine	0-6	10,208	50	2 (-35, 29)	71	88 (85, 90)
		≥7	36,500	114	37 (19, 50)	138	93 (92, 94)
	BNT162b2	0-6	8,461	42	2 (-39, 30)	64	87 (83, 90)
		≥7	30,269	106	34 (16, 49)	116	93 (91, 94)
	mRNA-1273	0-6	1,747	8	5 (-94, 54)	7	93 (86, 97)
		≥7	6,231	8	59 (16, 80)	22	93 (90, 96)

Figure 1. Vaccine effectiveness against infection by Omicron or Delta among adults aged ≥18 years by time since latest dose

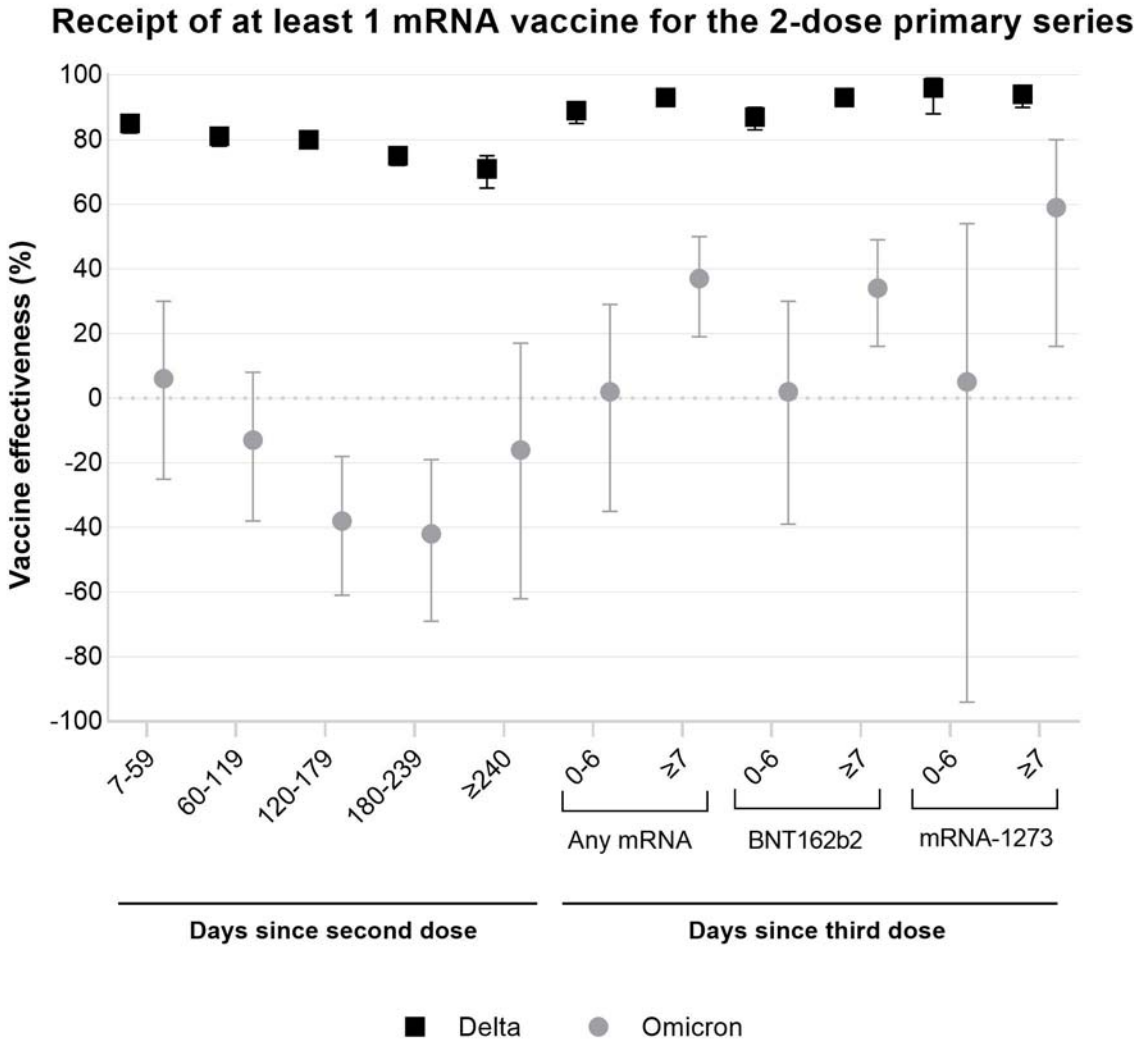


Exhibit F

The Journal of Infectious Diseases

MAJOR ARTICLE

Longitudinal Assessment of Diagnostic Test Performance Over the Course of Acute SARS-CoV-2 Infection

Rebecca L. Smith,[1,2,3] Laura L. Gibson,[4] Pamela P. Martinez,[1,5,6] Ruian Ke,[7] Agha Mirza,[8] Madison Conte,[8] Nicholas Gallagher,[9] Abigail Conte,[10] Leyi Wang,[11] Richard Fredrickson,[11] Darci C. Edmonson,[1] Melinda E. Baughman,[1] Karen K. Chiu,[1] Hannah Choi,[1] Tor W. Jensen,[1,12] Kevin R. Scardina,[1] Shannon Bradley,[1] Stacy L. Gloss,[1] Crystal Reinhart,[1] Jagadeesh Yedetore,[1] Alyssa N. Owens,[13] John Broach,[14,15] Bruce Barton,[16,17] Peter Lazar,[16] Darcy Henness,[18] Todd Young,[18] Alastair Dunnett,[18] Matthew L. Robinson,[8] Heba H. Mostafa,[9] Andrew Pekosz,[10] Yukari C. Manabe,[8] William J. Heetderks,[19] David D. McManus,[20] and Christopher B. Brooke[1,5]

[1]Carl R. Woese Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [2]Department of Pathobiology, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [3]Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [4]Division of Infectious Diseases and Immunology, Departments of Medicine and Pediatrics, University of Massachusetts Medical School, Worcester, Massachusetts, USA, [5]Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [6]Department of Statistics, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [7]T-6, Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, New Mexico, USA, [8]Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA, [9]Division of Medical Microbiology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [10]W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, [11]Veterinary Diagnostic Laboratory, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [12]Cancer Center at Illinois, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA, [13]Center for Clinical and Translational Research, University of Massachusetts Medical School, Worcester, Massachusetts, USA, [14]UMass Memorial Medical Center, Worcester, Massachusetts, USA, [15]Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, USA, [16]Division of Biostatistics and Health Services Research, University of Massachusetts Medical School, Worcester, Massachusetts, USA, [17]Department of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts, USA, [18]Carle Foundation Hospital, Urbana, Illinois, USA, [19]National Institute for Biomedical Imaging and Bioengineering, Bethesda, Maryland, USA, and [20]Division of Cardiology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Background. Serial screening is critical for restricting spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by facilitating timely identification of infected individuals to interrupt transmission. Variation in sensitivity of different diagnostic tests at different stages of infection has not been well documented.

Methods. In a longitudinal study of 43 adults newly infected with SARS-CoV-2, all provided daily saliva and nasal swabs for quantitative reverse transcription polymerase chain reaction (RT-qPCR), Quidel SARS Sofia antigen fluorescent immunoassay (FIA), and live virus culture.

Results. Both RT-qPCR and Quidel SARS Sofia antigen FIA peaked in sensitivity during the period in which live virus was detected in nasal swabs, but sensitivity of RT-qPCR tests rose more rapidly prior to this period. We also found that serial testing multiple times per week increases the sensitivity of antigen tests.

Conclusions. RT-qPCR tests are more effective than antigen tests at identifying infected individuals prior to or early during the infectious period and thus for minimizing forward transmission (given timely results reporting). All tests showed >98% sensitivity for identifying infected individuals if used at least every 3 days. Daily screening using antigen tests can achieve approximately 90% sensitivity for identifying infected individuals while they are viral culture positive.

Keywords. SARS-CoV-2; diagnostic testing; antigen testing; RT-qPCR testing; test sensitivity.

Frequent rapid diagnostic testing is critical for restricting community spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by allowing the timely identification and isolation of infected individuals to interrupt the chain of transmission. Quantitative reverse transcription polymerase chain reaction (RT-qPCR)-based detection of viral RNA within nasal swab or saliva samples represents the gold standard for sensitivity in detecting the presence of SARS-CoV-2. Unfortunately, it has been difficult to achieve high testing frequency and volume with the rapid reporting of results needed to mitigate transmission effectively due to supply shortages, cost, and infrastructure limitations.

There is considerable interest in the potential of rapid, lateral flow antigen tests to expand diagnostic testing capacity due to their ease of use, availability, relatively low cost, and rapid time to results [1]. However, data for their use in screening asymptomatic individuals is sparse [2]. Enthusiasm for their widespread deployment has been further tempered by well-publicized examples of false-positive results in people with low pretest probability of infection, and by reports suggesting they lack sensitivity compared with RT-qPCR, potentially making them less effective at mitigating community spread [3–5].

To maximize the effectiveness of available testing resources, there is an urgent need to quantify the sensitivities of different

Received 21 April 2021; editorial decision 18 June 2021; accepted 22 June 2021; published online June 30, 2021.

Correspondence: Christopher Brooke, PhD, 390 Burrill Hall, Urbana, IL 61801 (cbrooke@illinois.edu).

The Journal of Infectious Diseases® 2021;224:976–82

https://doi.org/10.1093/infdis/jiab337

testing platforms at different stages of infection and define how sensitivity can be enhanced through serial testing. To address this, we compared the sensitivities of nasal and saliva RT-qPCR tests with the Quidel Sofia SARS Antigen Fluorescent Immunoassay (FIA) over the course of mild or asymptomatic acute SARS-CoV-2 infection through daily sampling of individuals enrolled early during infection. We also estimated the effects of varying serial testing frequency on the sensitivities of both RT-qPCR and antigen tests.

METHODS

This study was approved by the Western Institutional Review Board, and all participants provided informed consent.

Participants

All on-campus students and employees of the University of Illinois at Urbana-Champaign are required to submit saliva for RT-qPCR testing every 2–4 days as part of the SHIELD campus surveillance testing program. Those testing positive are instructed to isolate, and were eligible to enroll in this study for a period of 24 hours following receipt of their positive test result. Close contacts of individuals who test positive (particularly those cohoused with them) are instructed to quarantine and were eligible to enroll for up to 5 days after their last known exposure to an infected individual. All participants were also required to have a documented negative saliva RT-qPCR result 7 days prior to enrollment in the study.

Individuals were recruited via either a link shared in an automated text message providing isolation information sent within 30 minutes of a positive test result, a call from a study recruiter, or a link shared by an enrolled study participant or included in information provided to all quarantining close contacts. In addition, signs were used at each testing location and a website was available to inform the community about the study.

Participants were required to be at least 18 years of age, have a valid university identity, speak English, have internet access, and live within 8 miles of the university campus. After enrollment and consent, participants completed an initial survey to collect information on demographics and health history, including suspected date of SARS-CoV-2 exposure. They were then provided with sample collection supplies.

Participants who tested positive prior to enrollment or during quarantine were followed for up to 14 days. Quarantining participants who continued to test negative by saliva RT-qPCR were followed for up to 7 days after their last exposure. All participants' data and survey responses were collected in the Eureka digital study platform.

Sample Collection

Each day, participants were remotely observed by study staff collecting:

1. 2 mL of saliva into a 50mL conical tube
2. 1 nasal swab from a single nostril using a foam-tipped swab that was placed within a dry collection tube
3. 1 nasal swab from the other nostril using a flocked swab that was subsequently placed in a collection vial containing viral transport medium (VTM).

The order of nostrils (left vs right) used for the 2 different swabs was randomized. For nasal swabs, participants were instructed to insert the soft tip of the swab at least 1 cm into the indicated nostril until they encountered mild resistance, rotate the swab around the nostril 5 times, leaving it in place for 10–15 seconds. After daily sample collection, participants completed a symptom survey. A courier collected all participant samples within 1 hour of collection using a no-contact pickup protocol designed to minimize courier exposure to infected participants. All study protocols were consistent throughout the duration of the study.

Saliva RT-qPCR

After collection, saliva samples were stored at room temperature and RT-qPCR was run within 12 hours of initial collection. The protocol for direct saliva to RT-qPCR assay used has been detailed previously [6]. In brief, saliva samples were heated at 95°C for 30 minutes, followed by the addition of 2× Tris/borate/EDTA buffer (TBE) at a 1:1 ratio (final concentration 1× TBE) and Tween-20 to a final concentration of 0.5%. Samples were assayed using the Thermo Taqpath coronavirus disease 2019 (COVID-19) assay.

Quidel Assay

Foam-tipped nasal swabs were placed in collection tubes, transported with cold packs, and stored at 4°C overnight based on guidance from the manufacturer. The morning after collection, swabs were run through the Sofia SARS antigen FIA on Sofia 2 devices according to the manufacturer's protocol.

Nasal Swab RT-qPCR

Collection tubes containing VTM and flocked nasal swabs were stored at −80°C after collection and were subsequently shipped to Johns Hopkins University for RT-qPCR and viral culture. After thawing, VTM was aliquoted for RT-qPCR and infectivity assays. One ml of VTM from the nasal swab was assayed on the Abbott Alinity per manufacturer's instructions in a College of American Pathologist and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

Nasal Virus Culture

VeroTMPRSS2 cells were grown in complete medium consisting of Dulbecco's Modified Eagle's Medium (DMEM) with 10% fetal bovine serum (Gibco), 1 mM glutamine (Invitrogen), 1 mM sodium pyruvate (Invitrogen), 100 U/mL of penicillin (Invitrogen), and 100 μg/mL of streptomycin (Invitrogen) [7]. Viral infectivity

was assessed on VeroTMPRSS2 cells as previously described using infection medium (identical to complete medium except the fetal bovine serum was reduced to 2.5%) [8]. When a cytopathic effect was visible in >50% of cells in a given well, the supernatant was harvested. The presence of SARS-CoV-2 was confirmed through RT-qPCR as described previously by extracting RNA from the cell culture supernatant using the Qiagen viral RNA isolation kit and performing RT-qPCR using the N1 and N2 SARS-CoV-2-specific primers and probes in addition to primers and probes for human RNaseP gene using synthetic RNA target sequences to establish a standard curve [9].

Data Analysis

At the time of analysis, nasal samples from 51 participants had been analyzed by virus culture and RT-qPCR. Eight individuals were removed from the analysis because their nasal virus culture was never positive, leaving 43 remaining participants. All confidence intervals around sensitivity were calculated using binconf from the Hmisc package in R version 3.6.2.

The sensitivity of each of the tests was analyzed in 3 ways. First, we calculated the daily sensitivity of each test across the course of the infection. Daily sensitivity was defined as the ability of each test (antigen, saliva RT-qPCR, or nasal RT-qPCR) to detect an infected person on a particular day, with day 0 defined as the day of first positive viral culture. Daily sensitivity was not calculated for time points with fewer than 5 observed person-days.

Second, we calculated the ability of each test to detect an infected person according to their viral culture status (status sensitivity). Viral culture status was defined as prepositive on days prior to the first positive viral culture result, positive on days for which viral culture results were positive, and postpositive on days with negative viral culture results that occurred after the first positive culture result. Status sensitivity was defined as the proportion of person-days with a positive result.

Finally, we calculated the ability of repeated testing over a 14-day period to detect an infected person (protocol sensitivity) using a value-of-information approach. Seven different testing frequencies were considered: daily, every other day, every third day, and so on, up to weekly sampling. For each individual, the result of testing on a given schedule was calculated for each potential starting date, with test results interpreted in parallel (all tests must be negative to be considered negative). For instance, each person contributed 2 observations to the every other day schedule, one starting on the first day of the study and comprising samples from days 1, 3, 5, 7, 9, 11, and 13, and the other starting on the second day of the study and comprising samples from days 2, 4, 6, 8, 10, 12, and 14. As each testing schedule was evaluated at each potential starting day, the number of potential schedules increased as testing frequency decreased. Protocol sensitivity was defined for individual testing schedules, where the numerator was the number of testing schedules resulting in at least 1 positive test and the denominator was the number of testing schedules examined, where a testing schedule was defined as a set of samples from 1 participant taken at a given frequency. The proportion of observations (or sets of samples) with a positive result (at least 1 positive test in the sampling time frame) was considered to be the sensitivity of that testing protocol (test and frequency combination).

Sensitivities were considered significantly different at $P < .05$. All statistics were calculated using binom.test or glm in R. All code used in analyses can be found at https://github.com/rlsdvm/CovidDetectAnalysis.

RESULTS

Table 1 shows demographic information for study participants reported here. The majority of participants (30/43, 69.8%) were non-Hispanic white and the average age was 32.3 years (SD 12.8; range, 19–73). Of the 43 participants, 23 provided 14 days of observations, 10 provided 13 days of observation, and only 3 provided fewer than 10 days of observation.

The estimated daily sensitivities of nasal and saliva RT-qPCR and antigen tests relative to the day of first nasal swab viral culture positivity, which was used as a surrogate marker of infectious virus shedding, are shown in Figure 1 and Supplementary Table 1. For all 3 tests, daily and status sensitivity peaked during days in which infectious virus shedding was detectable, as would be expected. Antigen test daily sensitivity declined precipitously after infectious virus could no longer be detected in nasal swabs, dropping to 0.238 (95% confidence interval [CI], .135–.385) within a week after the onset of culture positivity, which was significantly lower ($P < .001$) than both nasal and saliva RT-qPCR platforms. Nasal and saliva RT-qPCR only

Table 1. Demographic Information on Study Participants

Variable	Data (n = 43)
Age, y, mean (SD)	33.1 (12.8)
Race, No. (%)	
Native American	0 (0.0)
Asian	1 (2.3)
Black	4 (9.3)
Other	4 (9.3)
Pacific Islander	0 (0.0)
White	34 (79.1)
Sex, No. (%)	
Female	20 (46.5)
Male	23 (53.5)
Ethnicity, No. (%)	
Hispanic	8 (18.6)
Non-Hispanic	35 (81.4)

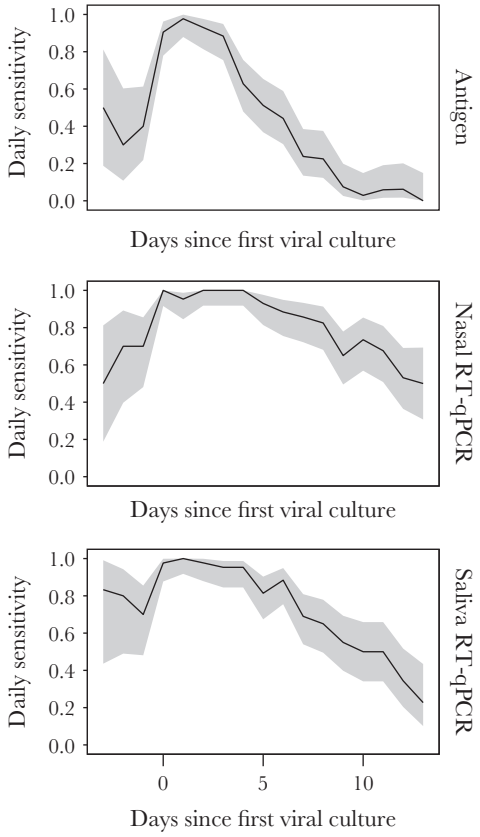


Figure 1. Daily sensitivity of each test platform relative to the day of first positive viral culture result. Shaded areas represent the 95% confidence interval around the observed proportion. Abbreviation: RT-qPCR, quantitative reverse transcription polymerase chain reaction.

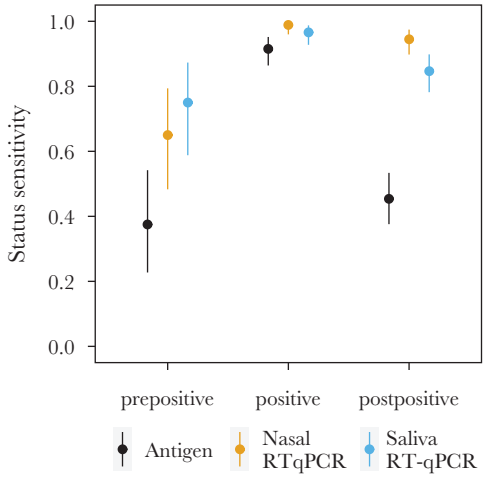


Figure 2. Status sensitivity of each test platform relative to viral culture positivity. Bars indicate the 95% confidence interval around the observed proportion. Prepositive (n = 31) refers to samples taken on days before the first viral culture-positive sample collected from each individual. Positive (n = 153) refers to samples taken on days for which viral culture results were positive. Postpositive (n = 126) refers to samples taken on days with negative viral culture results that occur after the first positive culture result. Abbreviation: RT-qPCR, quantitative reverse transcription polymerase chain reaction.

showed minor decreases in sensitivity during this period, remaining at 0.857 (95% CI, .722–.933) and 0.690 (95% CI, .540–.809) after a week, respectively, and were not significantly different from each other ($P = .07$).

We also used the viral culture data to measure the status sensitivities of each test before, during, and after viral shedding (Figure 2). Prior to the first day of detectable shedding of infectious virus, nasal RT-qPCR tests had significantly higher ($P < .05$) sensitivity (0.650; 95% CI, .483–.794) than the antigen test (0.375; 95% CI, .227–.542). The sensitivity of saliva RT-qPCR (0.750; 95% CI, .588–.873) was not significantly different from that of nasal RT-qPCR ($P = .14$) or antigen ($P = .07$) prior to the first positive viral culture. On days when the viral culture was positive, there were no significant differences in sensitivity among the 3 testing modalities ($P > .2$). After viral culture was no longer positive, the sensitivity of the antigen test (0.454; 95% CI, .376–.534) was significantly lower ($P < .001$) than the sensitivity of the saliva (0.847; 95% CI, .782–.898) or nasal (0.945; 95% CI, .898–.974) RT-qPCR tests.

We next estimated the protocol sensitivities, or how the ability of each of test platform to detect infected individuals was affected by differences in testing frequencies (Table 2 and Figure 3). In Figure 3A we show sensitivity to detect infected individuals at any stage of infection. For all 3 test platforms examined, protocol sensitivity remained >0.98 with testing at least every third day. When applied weekly, protocol sensitivity remained very high for nasal RT-qPCR at 0.987 (95% CI, .966–.996) and for saliva RT-qPCR at 0.963 (95% CI, .936–.982), but dropped to only 0.797 (95% CI, .747–.841) for the antigen test, which was significantly lower than either PCR test ($P < .001$).

When we compared the abilities of different testing frequencies to identify individuals before or during the period when infectious virus was detectable in nasal samples (Figure 3B), we observed a clear reduction in protocol sensitivity for all testing modalities when testing frequencies decreased below daily, although the linear trend was not statistically significant ($P > 0.05$). The reduction in protocol sensitivity was most pronounced for the antigen test, which dropped to 0.739 (95% CI, .634–.827) with testing every fourth day. However, both RT-qPCR tests were only slightly better with both showing a sensitivity of 0.784 (95% CI, .684–.865) for nasal and of 0.761 (95% CI, .659–.846) for saliva.

DISCUSSION

This is the first study to compare the longitudinal performance of rapid antigen and RT-qPCR tests with infectious virus shedding through daily testing early during SARS-CoV-2 infection.

Table 2. Protocol Sensitivity of Each Testing Platform to Detect an Infected Person During a 14-day Testing Period Relative to the Frequency of Testing

			Nasal Antigen				Saliva RT-qPCR				Nasal RT-qPCR			
			Probability of Detection		No. Positive		Probability of Detection		No. Positive		Probability of Detection		No. Positive	
Testing Frequency	No.	No. Before or While VC+[a]	Any Time[b]	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+
Daily	43	22	1	0.909	43	20	1	0.955	43	21	1	1	43	22
Every other day	86	44	1	0.841	86	37	0.988	0.909	85	40	1	0.909	86	40
Every third day	129	66	1	0.803	129	53	0.984	0.833	127	55	1	0.848	129	56
Every fourth day	172	88	0.959	0.739	165	65	0.983	0.761	169	67	1	0.784	172	69
Every fifth day	215	110	0.921	0.682	198	75	0.981	0.709	211	78	0.995	0.727	214	80
Every sixth day	258	132	0.864	0.621	223	82	0.965	0.644	249	85	0.992	0.667	256	88
Weekly	301	154	0.797	0.558	240	86	0.963	0.597	290	92	0.987	0.597	297	92

Abbreviations: RT-qPCR, quantitative reverse transcription polymerase chain reaction; VC+, viral culture positive,

[a]Before or while VC+ refers to detection of the individual before or during the time in which their viral culture was positive.

[b]Any time refers to detection of the individual at any point in the 14-day testing period.

Our data clearly define how the sensitivities of RT-qPCR and antigen tests vary over the course of SARS-CoV-2 infection. Prior to the presumed infectious period (here defined as the period during which infectious virus could be detected in nasal swab samples), the daily sensitivities of nasal and saliva RT-qPCR tests were substantially higher than that of the Quidel Sofia SARS Antigen FIA, suggesting that RT-qPCR tests will be more effective than antigen tests at identifying infected individuals before they can transmit to others, provided that results reporting is rapid enough.

Both RT-qPCR and antigen tests peaked in daily and status sensitivities when infectious virus was detectable in nasal swab samples, suggesting that all 3 modalities can be effective at identifying individuals during the presumed infectious period. After this period, the daily sensitivity of RT-qPCR tests decreased gradually, consistent with the dynamics described previously for RT-qPCR [10, 11]. In contrast, the daily sensitivity of the antigen test declined very quickly, suggesting that this test will be less effective at identifying individuals during later stages of infection. The short duration of antigen positivity may limit diagnosis and contact-tracing efforts in test-limited environments.

Previous studies have suggested that frequent testing would maximize the ability of a given test modality to detect infected individuals at any stage of infection [12–14]. We found that all testing modalities showed >98% protocol sensitivity to detect infection if used at least every 3 days, which supports that conjecture. However, the results presented here are based on empirical data, rather than the modeling approaches previously used, and therefore give stronger confidence to these estimates.

Altogether, these data demonstrate the importance of frequent testing regardless of test modality for identifying individuals while they are contagious. It should be noted that while virus culture on nasal swabs represents the best proxy available for infectivity, it is likely imperfect. It is also possible that some samples taken from infectious individuals may have given negative results in the virus culture assay because they were below the limit of detection, especially given that the viral culture samples were subjected to a single freeze/thaw cycle prior to being assayed.

The sensitivities of particular testing protocols presented here assume that individuals will strictly adhere to these testing frequencies over time. This may be more feasible in more closed populations, such as schools or businesses, than in general public health settings where the population is more fluid. However, the results could also be applied at a personal level to assist concerned individuals in determining the best frequency at which to seek out testing. These results should not be applied to interpret the results of a single test outside the context of regular screening.

It should also be noted that participation in this study was limited to faculty, students, and staff of the University of Illinois at Urbana-Champaign, and that the participant population included here was primarily young, non-Hispanic white, and skewed slightly towards men. All infections were either mild or asymptomatic, and no participants were hospitalized for COVID-19. The limited demographic and clinical profiles of our study population must be considered when extending these results to groups with different risk profiles.

Altogether, our results indicate that frequent serial RT-qPCR testing with rapid results reporting is the optimal screening strategy for identifying asymptomatic or presymptomatic individuals before they can transmit the virus, thus mitigating community spread of SARS-CoV-2. In communities where serial RT-qPCR testing with rapid results reporting is not possible, then frequent serial antigen testing (at least every 3 days or twice weekly) represents the best alternative.

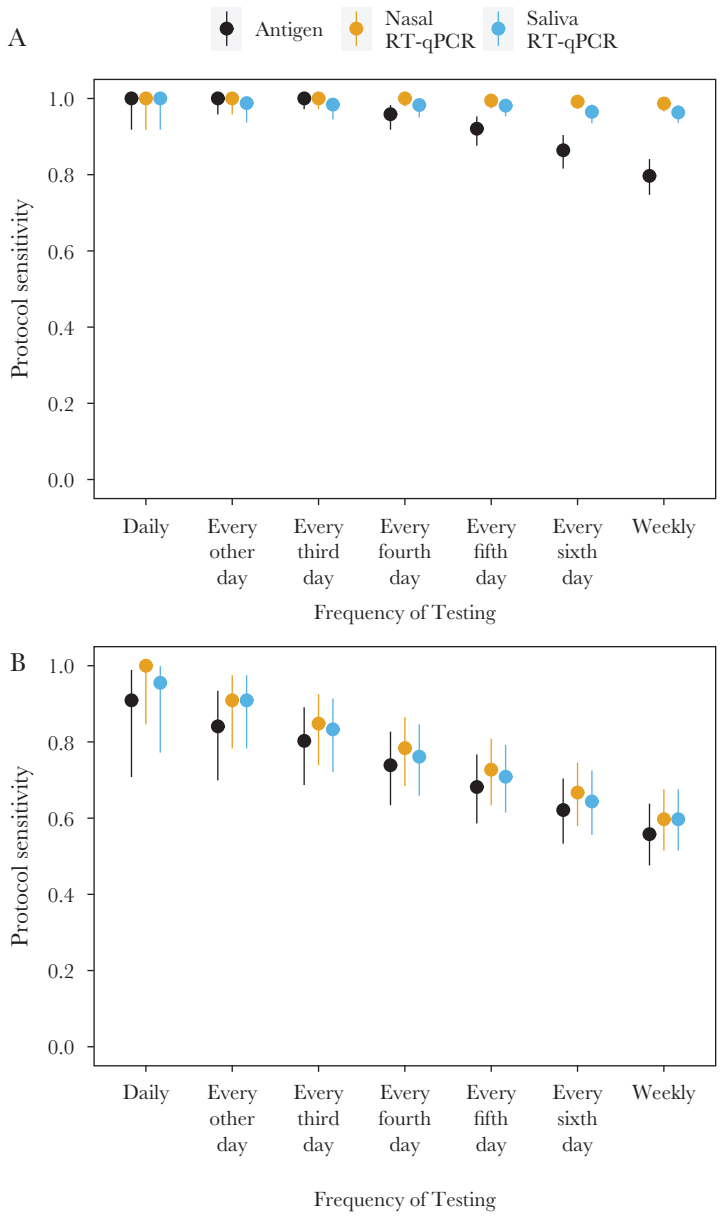


Figure 3. Protocol sensitivity of each test platform to detect an infected person (*A*) at any time over a 14-day testing period or (*B*) before or on days where nasal samples were viral culture positive, relative to the frequency of testing. Bars indicate 95% confidence interval around the observed proportion. Abbreviation: RT-qPCR, quantitative reverse transcription polymerase chain reaction.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank Shumon Ahmed, Carly Bell, Nate Bouton, Callie Brennen, Justin Brown, Coleco Buie, Emmaline Cler, Gary Cole, Trey Coleman, Lauren Engels, Savannah Feher, Kelsey Fox, Lexi Freeman, Yesenia Gonzalez, Montez Harris, Dan Hiser, Ayeshah Hussain, Daryl Jackson, Junko Jarrett, Michael Jenkins, Kalombo Kalonji, Syntyche Kanku, Steven Krauklis, Mary Krouse, Elmore Leshoure, Joe Lewis, Maggie Li, Angel Lopez, Guadalupe Lopez, Emily Luna, Chun Huai Luo, Colby Mackey, Skyler McLain, Yared Berhanu Melesse, Madison O'Donnell, Savanna Pflugmacher, Denver Piatt, Skyler Pierce, Jessica Quicksall, Gina Quitanilla, Ameera Samad, MacKenzie Scroggins, Monique Settles, Macie Sinn, Pete Varney, Evette Vlach, and Raeshun Williams-Chatman for their efforts supporting recruitment, enrollment, logistics, and sample collection. We also thank Jeffrey Olgin, Noah Peyser,

and Xochitl Butcher for assistance with the Eureka platform, Michelle Lore for assistance with REDcap, Melanie Loots for assistance with administration, Gillian Snyder for assistance in development of study protocols and logistics, and Erin Iturriaga and Jue Chen for study protocol development.

Disclaimer. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Institute of Biomedical Imaging and Bioengineering; the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services. Sofia 2 devices and associated supplies were provided to Carle Foundation Hospital by Quidel; however, Quidel played no role in the design of the study or the interpretation or presentation of the data.

Financial support. This work was supported by the National Heart, Lung, and Blood Institute at the National Institutes of Health (grant number 3U54HL143541-02S2) through the RADx-Tech program.

Potential conflicts of interest. C. B. B. and L. W. are listed as inventors on a pending patent application for the saliva RT-qPCR test used in this study. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Krüger LJ, Gaeddert M, Köppel L, et al. Evaluation of the accuracy, ease of use and limit of detection of novel, rapid, antigen-detecting point-of-care diagnostics for SARS-CoV-2. medRxiv, doi: 10.1101/2020.10.01.20203836, **4** October **2020**, preprint: not peer reviewed.
2. Pavelka M, Van-Zandvoort K, Abbott S, et al. The impact of population-wide rapid antigen testing on SARS-CoV-2 prevalence in Slovakia. Science **2021**; 372:635–41.
3. Jääskeläinen A, Ahava M, Jokela P, et al. Evaluation of three rapid lateral flow antigen detection tests for the diagnosis of SARS-CoV-2 infection. medRxiv, doi: 10.1101/2020.12.30.20249057, **4** January **2021**, preprint: not peer reviewed.
4. Moreno GK, Braun KM, Pray IW, et al. SARS-CoV-2 transmission in intercollegiate athletics not fully mitigated with daily antigen testing. Clin Infect Dis **2021**: ciab343. doi: 10.1093/cid/ciab343.
5. Pray IW, Ford L, Cole D, et al. Performance of an antigen-based test for asymptomatic and symptomatic SARS-CoV-2 testing at two university campuses—Wisconsin, September–October 2020. MMWR Morb Mortal Wkly Rep **2021**; 69:1642–7.
6. Ranoa DRE, Holland RL, Alnaji FG, et al. Saliva-based molecular testing for SARS-CoV-2 that bypasses RNA extraction. bioRxiv, doi: 10.1101/2020.06.18.159434, **18** June **2020**, preprint: not peer reviewed.
7. Matsuyama S, Nao N, Shirato K, et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A **2020**; 117:7001–3.
8. Pekosz A, Parvu V, Li M, et al. Antigen-based testing but not real-time polymerase chain reaction correlates with severe acute respiratory syndrome coronavirus 2 viral culture [published online ahead of print 20 January 2021]. Clin Infect Dis doi: 10.1093/cid/ciaa1706.
9. Waggoner JJ, Stittleburg V, Pond R, et al. Triplex real-time RT-PCR for severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis **2020**; 26:1633–5.
10. Kissler SM, Fauver JR, Mack C, et al. Viral dynamics of acute SARS-CoV-2 infection. medRxiv, doi: 10.1101/2020.10.21.20217042, **6** June **2021**, preprint: not peer reviewed.
11. Byrne AW, McEvoy D, Collins AB, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. BMJ Open **2020**; 10:e039856.
12. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 screening strategies to permit the safe reopening of college campuses in the United States. JAMA Netw Open **2020**; 3:e2016818.
13. Larremore DB, Wilder B, Lester E, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening. Sci Adv **2021**; 7:eabd5393.
14. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Ann Intern Med **2020**; 173:262–7.

Exhibit G

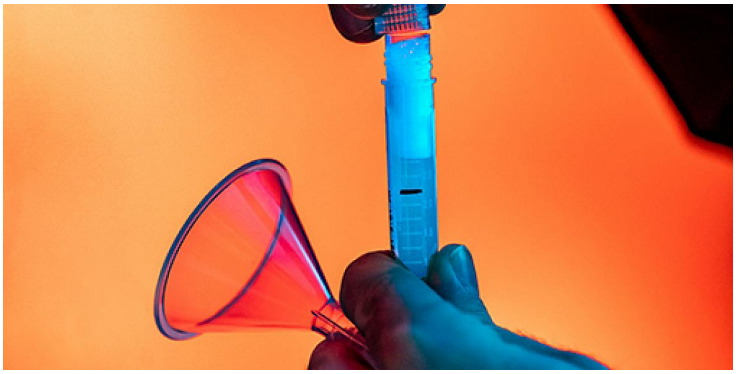
Wednesday, June 30, 2021

NIH-funded screening study builds case for frequent COVID-19 antigen testing

Rapid antigen tests perform on par with lab tests when used every three days.

Detecting SARS-CoV-2, the virus that causes COVID-19, improves with regularity of testing, whether using rapid antigen tests or PCR molecular tests. The PCR test is considered the gold standard for diagnosing COVID-19 infection, but cost and infrastructure issues, as well as wait times for PCR results, have limited its use more broadly as a screening tool for asymptomatic people because rapid results are needed to interrupt the chain of transmission.

In a highly anticipated study that compares rapid antigen and laboratory PCR approaches for COVID-19 serial screening, researchers affiliated with the National Institutes of Health's Rapid Acceleration of Diagnostics (RADx) initiative reported results from 43 people infected with the virus. They found that both testing methods were equally effective in detecting SARS-CoV-2 infection when tests were given on a regular cadence every three days. While individual PCR tests are more sensitive than antigen tests, particularly early in infection, the results showed that both testing approaches can give 98% sensitivity when taken regularly as part of a screening program. Because antigen tests at the point of care or at home can deliver immediate results and are less costly than laboratory tests, these results suggest that they could be a highly effective screening tool to prevent disease outbreaks.



A vial of saliva sample for SARS-CoV-2 testing. *Fred Zwicky, University of Illinois*

"Rapid antigen testing at home, two to three times per week, is a powerful and convenient way for individuals to screen for COVID-19 infection," said Bruce Tromberg, Ph.D., director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), part of NIH. "With schools and businesses reopening, an individual's risk of infection can change from day to day. Serial antigen testing can help people manage this risk and quickly take action to prevent spread of the virus."

Dr. Tromberg leads the RADx Tech program, which supported the study. For the past year, the RADx initiative has been a catalyst for dozens of diagnostic device technologies—including both antigen and PCR tests—accelerating the development and commercialization of COVID-19 diagnostic tests.

Authors of the study in the June 30, 2021, *Journal of Infectious Diseases*, are researchers at the University of Illinois at Urbana-Champaign (UIUC); University of Massachusetts Medical School, Worcester; Johns Hopkins School of Medicine, Baltimore; and NIBIB.

Employees and students at UIUC participate in SHIELD Illinois, a COVID-19 screening program implemented this past year on campus. SHIELD Illinois participants who tested positive or lived in close contact with a person who received a positive result were invited to participate in this research study. The goal was to investigate the sensitivity of specific types of diagnostic tests during infection by having participants take PCR and antigen tests daily during the course of their infection. Daily samples were also tested for the presence of infectious virus as a measure of how easily individuals may transmit virus to others at different stages of infection.

The team began their participant recruitment in early December 2020, which continued into spring 2021. To capture daily test results across the entire course of infection, participants were enrolled within days after their exposure to the virus, having received negative test results in the seven days prior to enrollment. None of the participants in the study experienced symptoms that required hospitalization.

Participants supplied a saliva sample and two forms of nasal swabs for 14 consecutive days. A courier retrieved the samples daily. To obtain a rough measure of the period during which subjects could spread infection to others, the research team sent one of the nasal samples to a laboratory at Johns Hopkins University to observe the growth of live virus in culture. Viral culture is labor- and cost-intensive and is not practical for testing large numbers of people but provides a high degree of certainty that live virus can be derived from the sample. By culturing samples in this study, the researchers could estimate the onset and duration of COVID-19 infectiousness.

"Antigen tests and PCR tests detect the presence of different molecules found in virus particles," explained Christopher B. Brooke, senior author and assistant professor of molecular and cell biology at UIUC. "Most tests detect genetic material associated with the virus, but that doesn't mean there is live virus there. The only way to tell with certainty if live, infectious virus is present is to perform an infectivity assay, or culture, such as was performed at the Johns Hopkins laboratory."

The researchers then compared three COVID-19 viral testing modalities — PCR testing of saliva, PCR testing of nasal samples and rapid antigen testing of nasal samples. The saliva sample results were performed with an authorized saliva-based PCR test developed at UIUC, called covidSHIELD, that can generate a result after about 12 hours. A separate PCR test performed with an Abbott Alinity device was used to obtain results from a nasal swab. Rapid antigen testing was performed using a Quidel Sofia SARS Antigen Fluorescent Immunoassay device that is authorized for use at the point of care and can generate a result after 15 minutes.

The researchers calculated the sensitivity of each test modality to detect SARS-CoV-2 and measured the presence of live virus over a two-week period following initial infection. They found that PCR molecular tests — both from saliva and nasal samples — are more sensitive than rapid antigen tests at detecting the SARS-CoV-2 virus prior to the infectious period. If the result from PCR tests could be quickly returned, the person receiving the result could undertake measures much sooner to prevent transmitting the virus to others. Unfortunately, results from PCR are rarely returned the day of testing.

The authors calculated test sensitivity based on test frequency, finding that a cadence of tests every three days achieved better than 98% sensitivity to detect infection, whether using rapid antigen tests or PCR tests. When they assessed frequency of testing once per week, nasal and saliva PCR testing sensitivity remained high, at around 98%, but antigen test sensitivity declined to 80%. These results show, for the first time, that testing at least twice per week with rapid antigen tests has comparable performance with PCR testing and maximizes the likelihood of detecting people infected with SARS-CoV-2.

The sensitivity of PCR molecular tests and rapid antigen tests is highest when viral cultures are positive for SARS-CoV-2, as might be expected. Even beyond this infectivity period, though, PCR tests continue to detect particles of virus, when the virus is most likely no longer transmissible.

"Silent transmission of the SARS-CoV-2 virus from individuals with no symptoms contributes significantly to the spread of the virus," said co-author William Heetderks, M.D., Ph.D., a RADx Tech program advisor at NIBIB. "Faster, cheaper and broader testing with antigen tests can be a big help in the kind of large-scale screening scenarios that can find these silent transmitters."

This study was funded by the NIH RADx-Tech program under 3U54HL143541-02S2.

About the National Institute of Biomedical Imaging and Bioengineering (NIBIB): NIBIB's mission is to improve health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating engineering and physical science with biology and medicine to advance our understanding of disease and its prevention, detection, diagnosis, and treatment. NIBIB supports emerging technology research and development within its internal laboratories and through grants, collaborations, and training. More information is available at the NIBIB website.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

NIH...Turning Discovery Into Health®

Article

Longitudinal assessment of diagnostic test performance over the course of acute SARS-CoV-2 infection. 2021. Journal of Infectious Diseases. DOI:10.1093/jid/jiab337.

###

Institute/Center

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

Contact

Ray MacDougall
301-451-7638

Connect with Us

- Subscribe to news releases
- RSS Feed

Exhibit H

The Washington Post
Democracy Dies in Darkness

‘The war has changed’: Internal CDC document urges new messaging, warns delta infections likely more severe

The internal presentation shows that the agency thinks it is struggling to communicate on vaccine efficacy amid increased breakthrough infections

By Yasmeen Abutaleb, Carolyn Y. Johnson and Joel Achenbach
July 29, 2021 at 8:58 p.m. EDT

The delta variant of the coronavirus appears to cause more severe illness than earlier variants and spreads as easily as chickenpox, according to an internal federal health document that argues officials must “acknowledge the war has changed.”

The document is an internal Centers for Disease Control and Prevention slide presentation, shared within the CDC and obtained by The Washington Post. It captures the struggle of the nation’s top public health agency to persuade the public to embrace vaccination and prevention measures, including mask-wearing, as cases surge across the United States and new research suggests vaccinated people can spread the virus.

The document strikes an urgent note, revealing the agency knows it must revamp its public messaging to emphasize vaccination as the best defense against a variant so contagious that it acts almost like a different novel virus, leaping from target to target more swiftly than Ebola or the common cold.

READ THE DOCUMENTS
Full PDF

It cites a combination of recently obtained, still-unpublished data from outbreak investigations and outside studies showing that vaccinated individuals infected with delta may be able to transmit the virus as easily as those who are unvaccinated. Vaccinated people infected with delta have measurable viral loads similar to those who are unvaccinated and infected with the variant.

“I finished reading it significantly more concerned than when I began,” Robert Wachter, chairman of the Department of Medicine at the University of California at San Francisco, wrote in an email.

CDC scientists were so alarmed by the new research that the agency earlier this week significantly changed guidance for vaccinated people even before making new data public.

The data and studies cited in the document played a key role in revamped recommendations that call for everyone — vaccinated or not — to wear masks indoors in public settings in certain circumstances, a federal health official said. That official told The Post that the data will be published in full on Friday. CDC Director Rochelle Walensky privately briefed members of Congress on Thursday, drawing on much of the material in the document.

One of the slides states that there is a higher risk among older age groups for hospitalization and death relative to younger people, regardless of vaccination status. Another estimates that there are 35,000 symptomatic infections per week among 162 million vaccinated Americans.

The document outlines “communication challenges” fueled by cases in vaccinated people, including concerns from local health departments about whether coronavirus vaccines remain effective and a “public convinced vaccines no longer work/booster doses needed.”

The presentation highlights the daunting task the CDC faces. It must continue to emphasize the proven efficacy of the vaccines at preventing severe illness and death while acknowledging milder breakthrough infections may not be so rare after all, and that vaccinated individuals are transmitting the virus. The agency must move the goal posts of success in full public view.

The CDC declined to comment.

“Although it’s rare, we believe that at an individual level, vaccinated people may spread the virus, which is why we updated our recommendation,” according to the federal health official, who spoke on the condition of anonymity because they were not authorized to speak publicly. “Waiting even days to publish the data could result in needless suffering and as public health professionals we cannot accept that.”

The presentation came two days after Walensky announced the reversal in guidance on masking among people who are vaccinated. On May 13, people were told they no longer needed to wear masks indoors or outdoors if they had been vaccinated. The new guidance reflects a strategic retreat in the face of the delta variant. Even people who are vaccinated should wear masks indoors in communities with substantial viral spread or when in the presence of people who are particularly vulnerable to infection and illness, the CDC said.

The document presents new science but also suggests a new strategy is needed on communication, noting that public trust in vaccines may be undermined when people experience or hear about breakthrough cases, especially after public health officials have described them as rare.

Matthew Seeger, a risk communication expert at Wayne State University in Detroit, said a lack of communication about breakthrough infections has proved problematic. Because public health officials had emphasized the great efficacy of the vaccines, the realization that they aren't perfect may feel like a betrayal.

"We've done a great job of telling the public these are miracle vaccines," Seeger said. "We have probably fallen a little into the trap of over-reassurance, which is one of the challenges of any crisis communication circumstance."

The CDC's revised mask guidance stops short of what the internal document calls for. "Given higher transmissibility and current vaccine coverage, universal masking is essential to reduce transmission of the Delta variant," it states.

The document makes clear that vaccination provides substantial protection against the virus. But it also states that the CDC must "improve communications around individual risk among [the] vaccinated" because that risk depends on a host of factors, including age and whether someone has a compromised immune system.

The document includes CDC data from studies showing that the vaccines are not as effective in immunocompromised patients and nursing home residents, raising the possibility that some at-risk individuals will need an additional vaccine dose.

The presentation includes a note that the findings and conclusions are those of the authors and do not necessarily represent the CDC's official position.

The internal document contains some of the scientific information that influenced the CDC to change its mask guidance. The agency faced criticism from outside experts this week when it changed the mask guidance without releasing the data, a move that violated scientific norms, said Kathleen Hall Jamieson, director of the Annenberg Public Policy Center at the University of Pennsylvania.

"You don't, when you're a public health official, want to be saying, 'Trust us, we know, we can't tell you how,'" Jamieson said. "The scientific norm suggests that when you make a statement based on science, you show the science. … And the second mistake is they do not appear to be candid about the extent to which breakthroughs are yielding hospitalizations."

The breakthrough cases are to be expected, the CDC briefing states, and will probably rise as a proportion of all cases because there are so many more people vaccinated now. This echoes data seen from studies in other countries, including highly vaccinated Singapore, where 75 percent of new infections reportedly occur in people who are partially and fully vaccinated.

The CDC document cites public skepticism about vaccines as one of the challenges: "Public convinced vaccines no longer work," one of the first slides in the presentation states.

Walter A. Orenstein, associate director of the Emory Vaccine Center, said he was struck by data showing that vaccinated people who became infected with delta shed just as much virus as those who were not vaccinated. The slide references an outbreak in Barnstable County, Mass., where vaccinated and unvaccinated people shed nearly identical amounts of virus.

“I think this is very important in changing things,” Orenstein said.

A person working in partnership with the CDC on investigations of the delta variant, who spoke on the condition of anonymity because they were not authorized to speak, said the data came from a July 4 outbreak in Provincetown, Mass. Genetic analysis of the outbreak showed that people who were vaccinated were transmitting the virus to other vaccinated people. The person said the data was “deeply disconcerting” and a “canary in the coal mine” for scientists who had seen the data.

If the war has changed, as the CDC states, so has the calculus of success and failure. The extreme contagiousness of delta makes herd immunity a more challenging target, infectious-disease experts said.

“I think the central issue is that vaccinated people are probably involved to a substantial extent in the transmission of delta,” Jeffrey Shaman, a Columbia University epidemiologist, wrote in an email after reviewing the CDC slides. “In some sense, vaccination is now about personal protection — protecting oneself against severe disease. Herd immunity is not relevant as we are seeing plenty of evidence of repeat and breakthrough infections.”

The document underscores what scientists and experts have been saying for months: It is time to shift how people think about the pandemic.

Kathleen Neuzil, a vaccine expert at the University of Maryland School of Medicine, said getting more people vaccinated remains the priority, but the public may also have to change its relationship to a virus almost certain to be with humanity for the foreseeable future.

“We really need to shift toward a goal of preventing serious disease and disability and medical consequences, and not worry about every virus detected in somebody’s nose,” Neuzil said. “It’s hard to do, but I think we have to become comfortable with coronavirus not going away.”

Exhibit I


The Washington Post

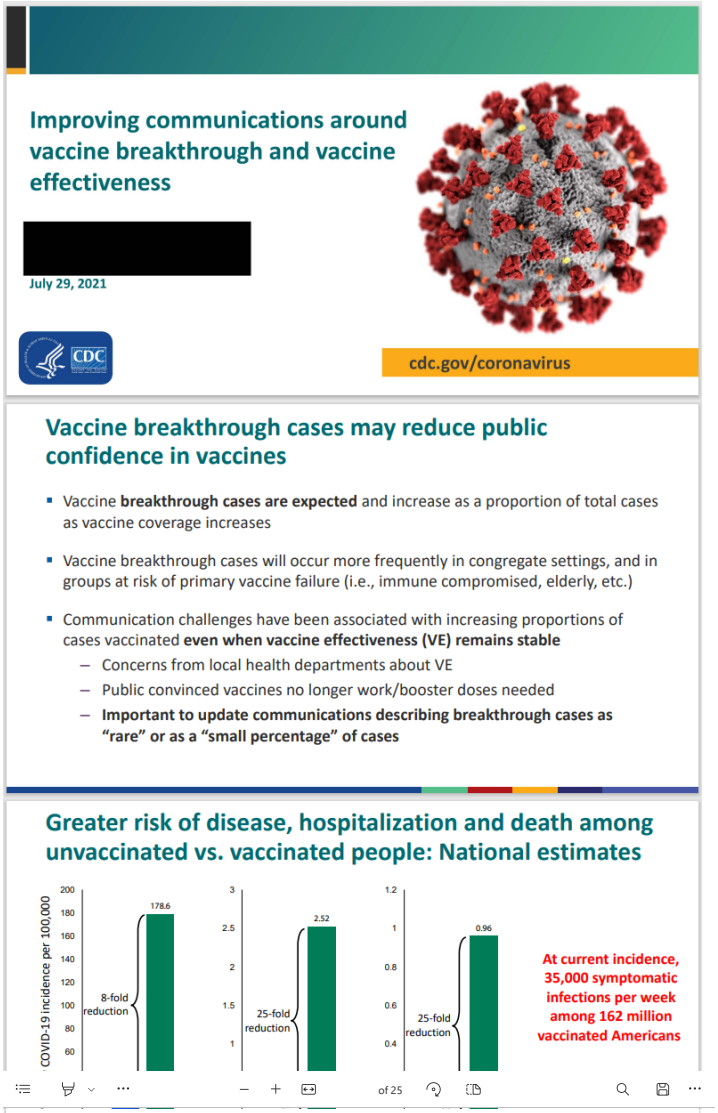
Health • Context

Read: Internal CDC document on breakthrough infections

Updated Jul 30, 2021 at 7:15 AM

An internal CDC document urges officials to “acknowledge the war has changed” and improve the public’s understanding of breakthrough infections. Read the story here.

Click here to download if the document isn't visible or legible.



Improving communications around vaccine breakthrough and vaccine effectiveness

[redacted]

July 29, 2021

cdc.gov/coronavirus

Vaccine breakthrough cases may reduce public confidence in vaccines

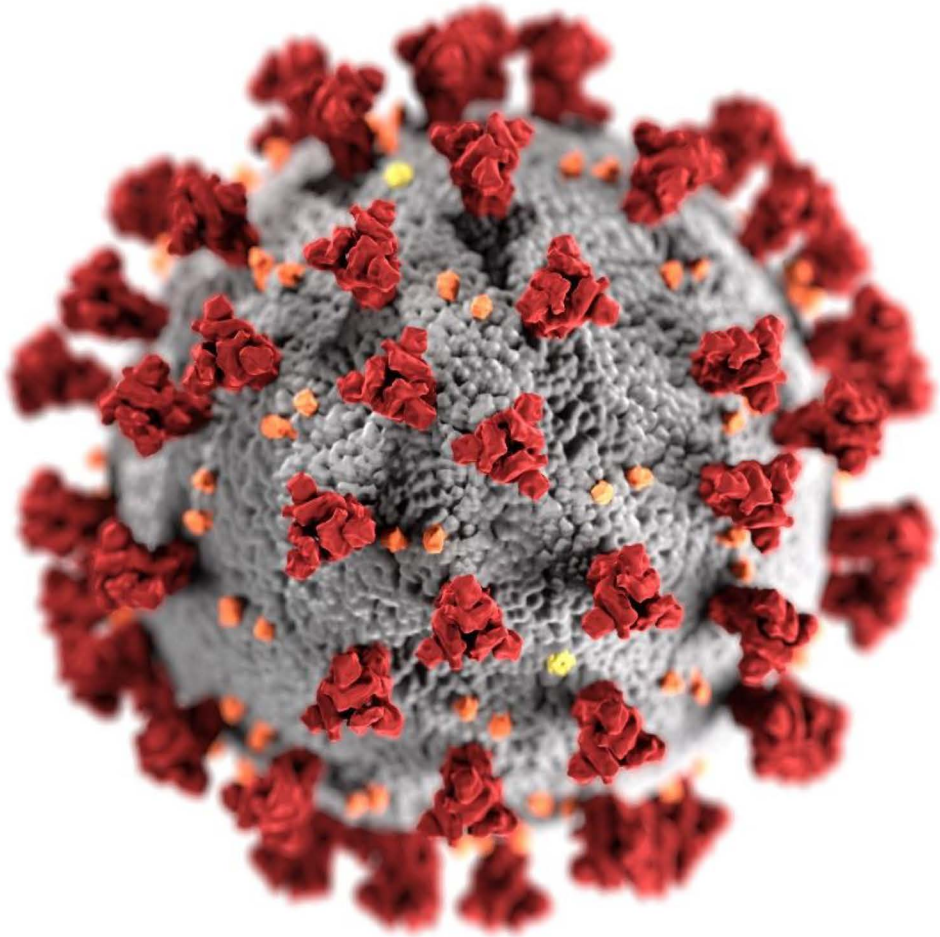
- Vaccine **breakthrough cases are expected** and increase as a proportion of total cases as vaccine coverage increases
- Vaccine breakthrough cases will occur more frequently in congregate settings, and in groups at risk of primary vaccine failure (i.e., immune compromised, elderly, etc.)
- Communication challenges have been associated with increasing proportions of cases vaccinated **even when vaccine effectiveness (VE) remains stable**
  - Concerns from local health departments about VE
  - Public convinced vaccines no longer work/booster doses needed
  - **Important to update communications describing breakthrough cases as “rare” or as a “small percentage” of cases**

Greater risk of disease, hospitalization and death among unvaccinated vs. vaccinated people: National estimates

Improving communications around vaccine breakthrough and vaccine effectiveness

[redacted]

July 29, 2021

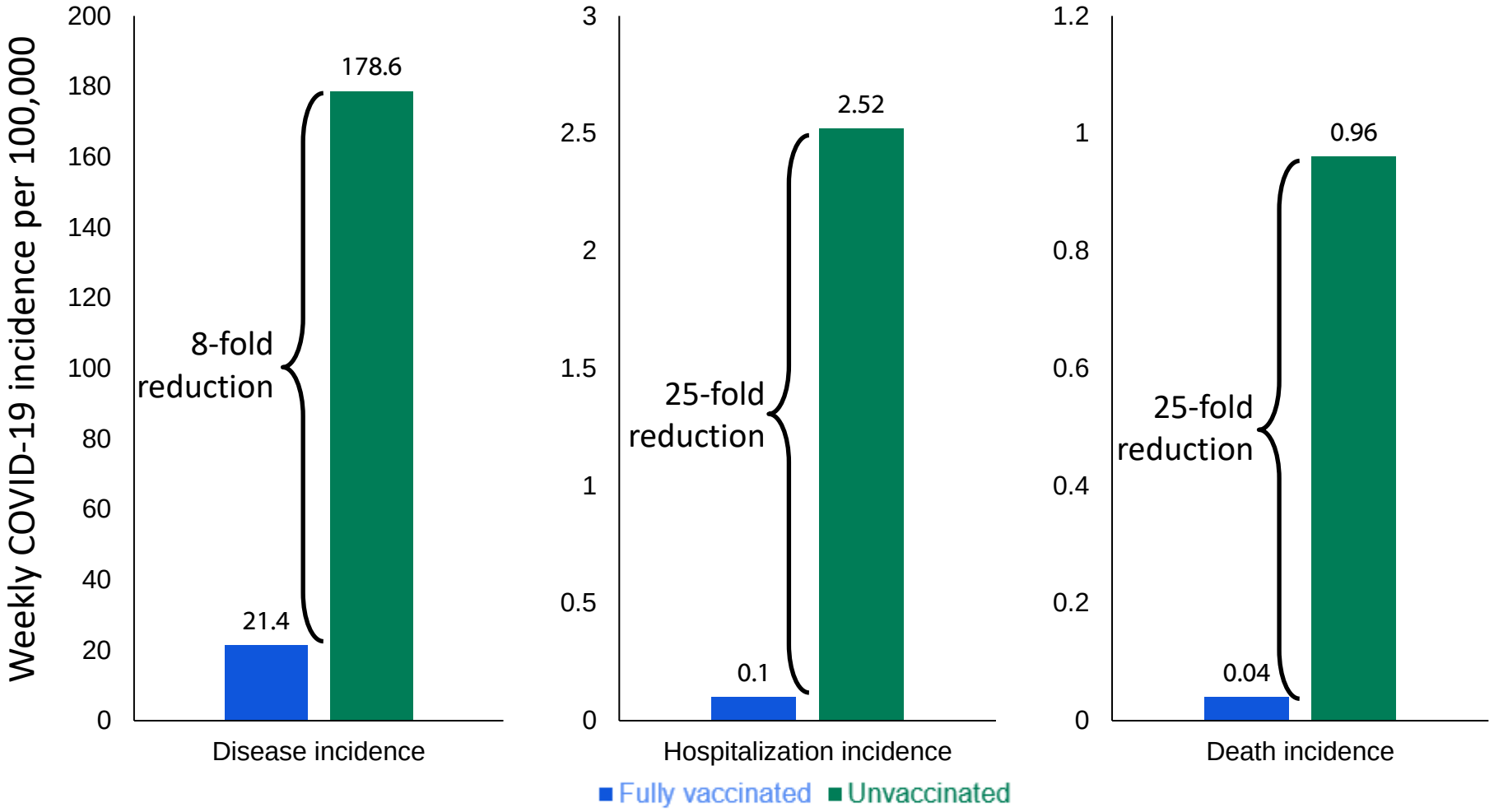


cdc.gov/coronavirus

Vaccine breakthrough cases may reduce public confidence in vaccines

- Vaccine **breakthrough cases are expected** and increase as a proportion of total cases as vaccine coverage increases
- Vaccine breakthrough cases will occur more frequently in congregate settings, and in groups at risk of primary vaccine failure (i.e., immune compromised, elderly, etc.)
- Communication challenges have been associated with increasing proportions of cases vaccinated **even when vaccine effectiveness (VE) remains stable**
  - Concerns from local health departments about VE
  - Public convinced vaccines no longer work/booster doses needed
  - **Important to update communications describing breakthrough cases as "rare" or as a "small percentage" of cases**

Greater risk of disease, hospitalization and death among unvaccinated vs. vaccinated people: National estimates

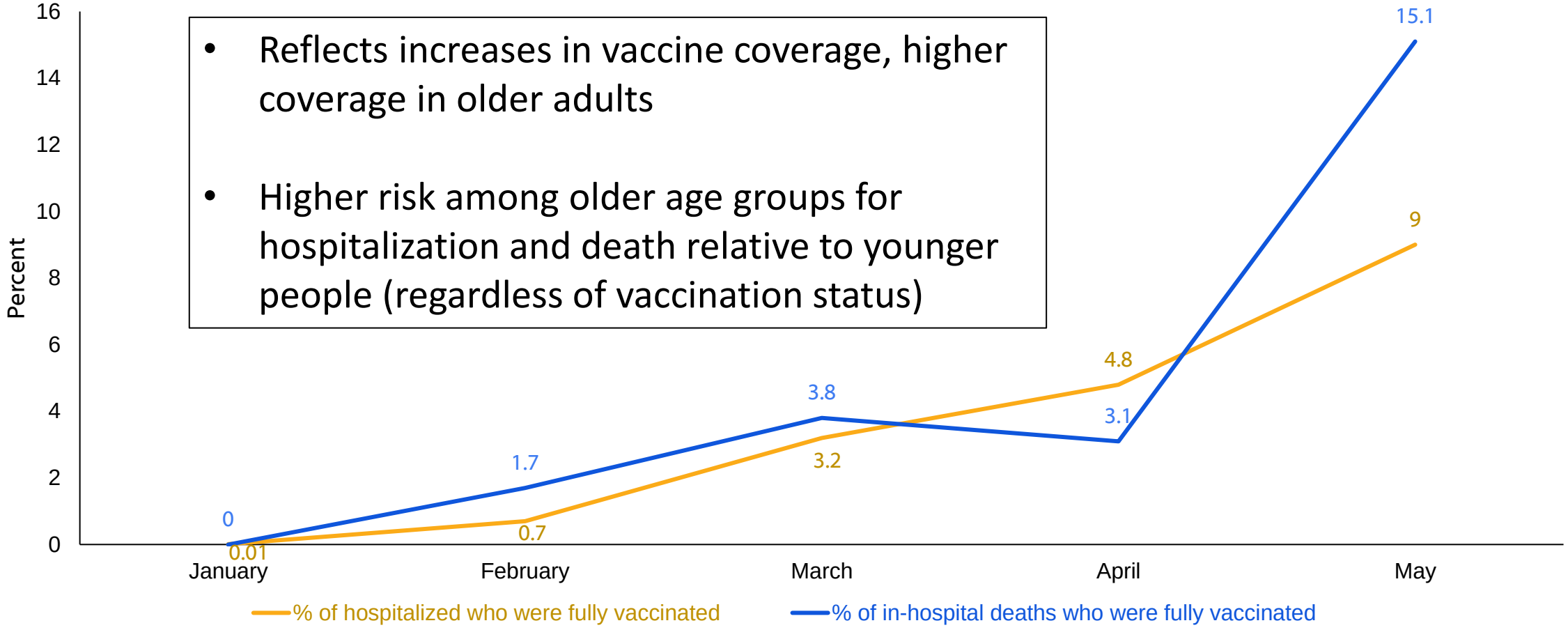


At current incidence, 35,000 symptomatic infections per week among 162 million vaccinated Americans

Data from COVID Tracker as of July 24, 2021. Average incidence 100 cases per 100,000 persons per week. Vaccine effectiveness against symptomatic illness = 88% (Lopez Bernal et al. NEJM 2021), where risk is [1 – VE] or 12%. Vaccine effectiveness hospitalization (or death) = 96% (Stowe et al. PHE preprint), where risk is [1 – VE] or 4%. Rate in unvaccinated = Community rate/((1-fully vaccinated coverage) + (1-VE)*fully vaccinated coverage). Rate in fully vaccinated=(1-VE)*Rate in unvaccinated. Fully vaccinated coverage proportions were from COVID Data Tracker as of July 24, 2021 (50% for US,).

Increasing percentage of vaccinated persons among those hospitalized in COVID-NET

- Reflects increases in vaccine coverage, higher coverage in older adults
- Higher risk among older age groups for hospitalization and death relative to younger people (regardless of vaccination status)



(CONFIDENTIAL – preliminary data, subject to change)

CDC uses multiple platforms and study designs to monitor COVID-19 vaccine effectiveness (VE)

VE priority	Design
Infection and transmission	Prospective cohort among healthcare personnel (HCP) & frontline workers; transmissibility evaluation in LTCF and other congregate settings; case-ascertained household cohorts for transmission
Non-severe disease	Test-negative design (TND) case-control among outpatients; Electronic health record (EHR) datasets
Severe disease/hospitalization	TND among hospitalized patients (for adults and children); conventional case-control using hospitalized controls; EHR datasets
Older adults, including nursing home residents	Case-control among adults ≥65 years; National Healthcare Safety Network comparison to population coverage estimated through immunization registries; Outbreaks in nursing homes; EHR datasets
Those with key underlying conditions (e.g., immunocompromised)	Captured above
Duration of protection	Captured above
Variant-specific VE	Captured above; outbreaks in congregate settings

VE results

Early evidence in health care providers that vaccination may reduce transmission and attenuate illness (HEROES/RECOVER)

- Period: December 14, 2020 – April 10, 2021
- VE against infection was **91%** (CI 76-97) among fully vaccinated; **81%** (CI 64-90) for partially vaccinated
- Compared to unvaccinated cases, vaccinated cases (full or partial) had:
  - 40% lower mean RNA viral load (2.3 v. 3.8 copies/mL)
  - shorter mean duration of detectable viral RNA (2.7 v. 8.9 days)
  - lower risk of febrile symptoms (25.0% v. 63.1%)
  - shorter mean duration of symptoms (10.3 v. 16.7 days)

Thompson et al. doi:10.1056/NEJMoa2107058

Preliminary VE estimates assessing duration of protection for 2 doses of mRNA vaccines

- VISION (test negative design across 8 integrated healthcare systems), data through June 22, 2021
  - VE against hospitalization **88%** (CI 86-90)
  - No evidence of waning immunity to 16 weeks post-2nd dose
- IVY3 (test negative design across 21 hospitals), data through June 2021
  - VE against hospitalization **87%** (CI 85-97)
  - No evidence of waning immunity through 20 weeks post-2nd dose
- Healthcare personnel (test negative design across 33 sites), data to May 31, 2021
  - VE against symptomatic infection **90%**
  - No evidence of waning immunity through 14 weeks post-2nd dose

(CONFIDENTIAL – preliminary data, subject to change)

Lower estimates of VE for mRNA vaccines among immunocompromised populations: Published evidence

- 71% (CI 37-87%) **against SARS-CoV-2 infection** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 90% (CI 83-96%) overall[1]
- 80% **against SARS-CoV-2 infection** ≥7 days after 2nd dose of mRNA vaccine among people with IBD on immunosuppressive medication[2]
- 75% (CI 44-88%) **against symptomatic COVID-19** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 94% (CI 87-97%) overall[1]
- 59% **against COVID-19 hospitalization** among immunocompromised ≥14 days after 2nd dose of mRNA vaccine[3] vs. 91% (CI 86-95%) without immune compromise[3]

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438; **2.** Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf; **3.** Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776

Lower estimates of mRNA vaccine effectiveness (VE) among nursing home residents

- VE of mRNA vaccines for any infection (including asymptomatic) was **65%–75%** in different locations and platforms during December 2020 – May 2021
  - NHSN: 70% (62-76) for Pfizer-BioNTech, 65% (51-75) for Moderna
  - Signature Healthcare: 74% (54-85) for mRNA vaccines
  - LA County: 75% (43-89) for Moderna

Vaccine effectiveness (VE) and breakthrough example using the screening method

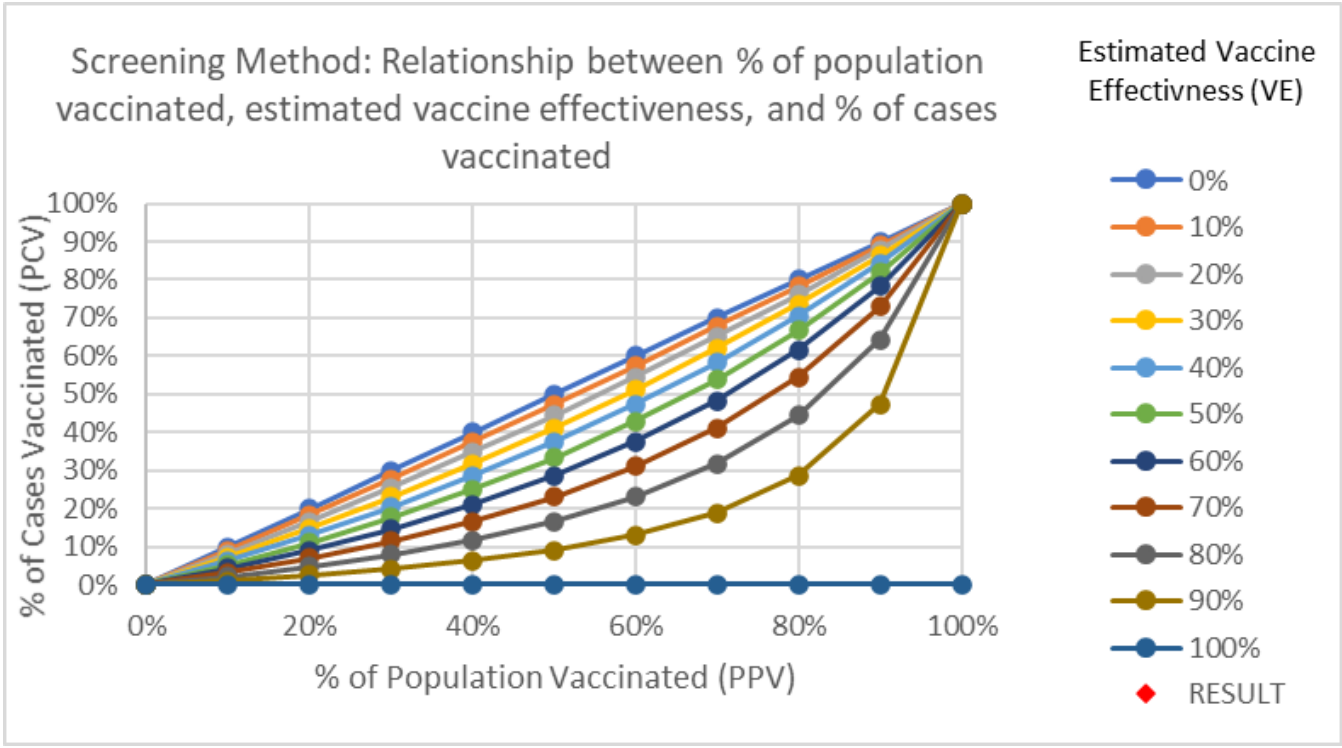
- **Screening method**

  Estimates VE by comparing vaccine coverage in cases to population

  VE = 1 – [(PCV/(1-PCV))((1-PPV)/PPV)]

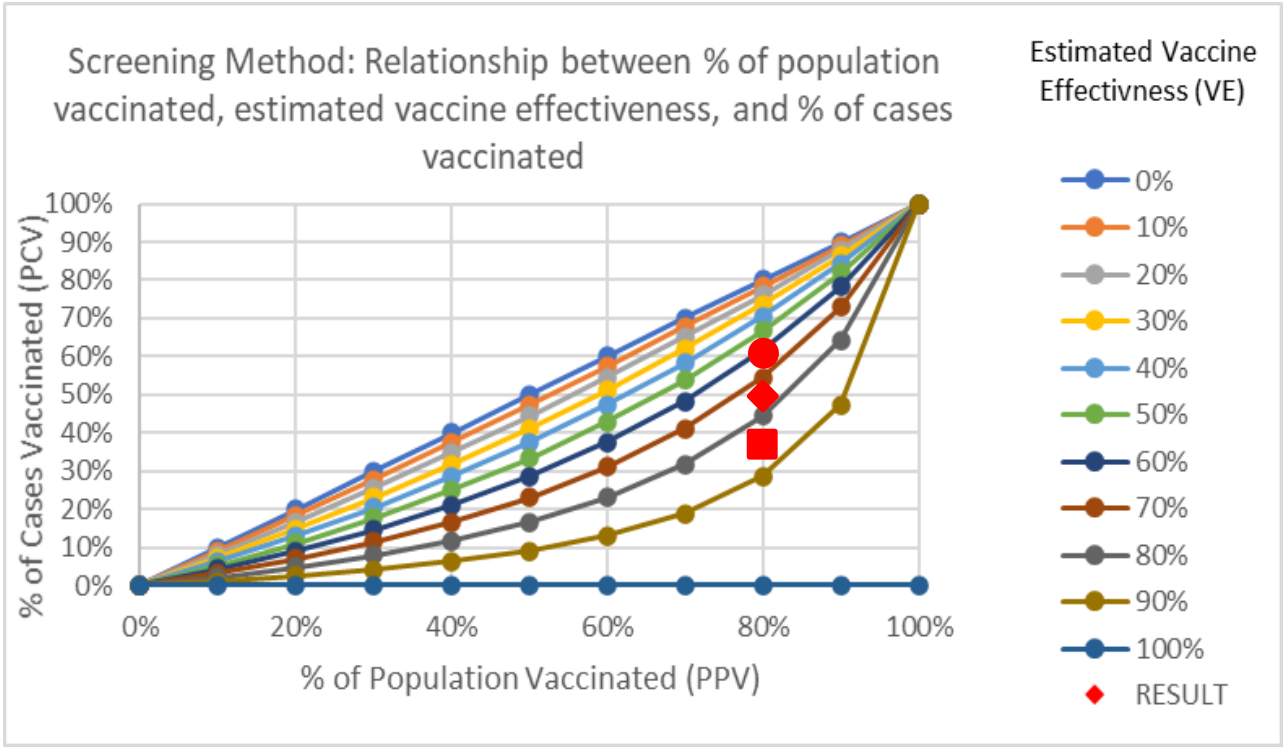
  - PCV=proportion cases vaccinated
  - PPV=proportion population vaccinated

- **Recent nursing home outbreak of Beta variant, VE estimate:**
  - 61% against infection
  - 75% against mild illness
  - 85% against severe illness



Vaccine breakthrough in LTCF residents where coverage is 80% nationally

- For infection (VE 61%), 61% of cases vaccinated
- For mild illness (VE 75%), 50% of cases vaccinated
- For severe illness (VE 85%), 38% of cases vaccinated

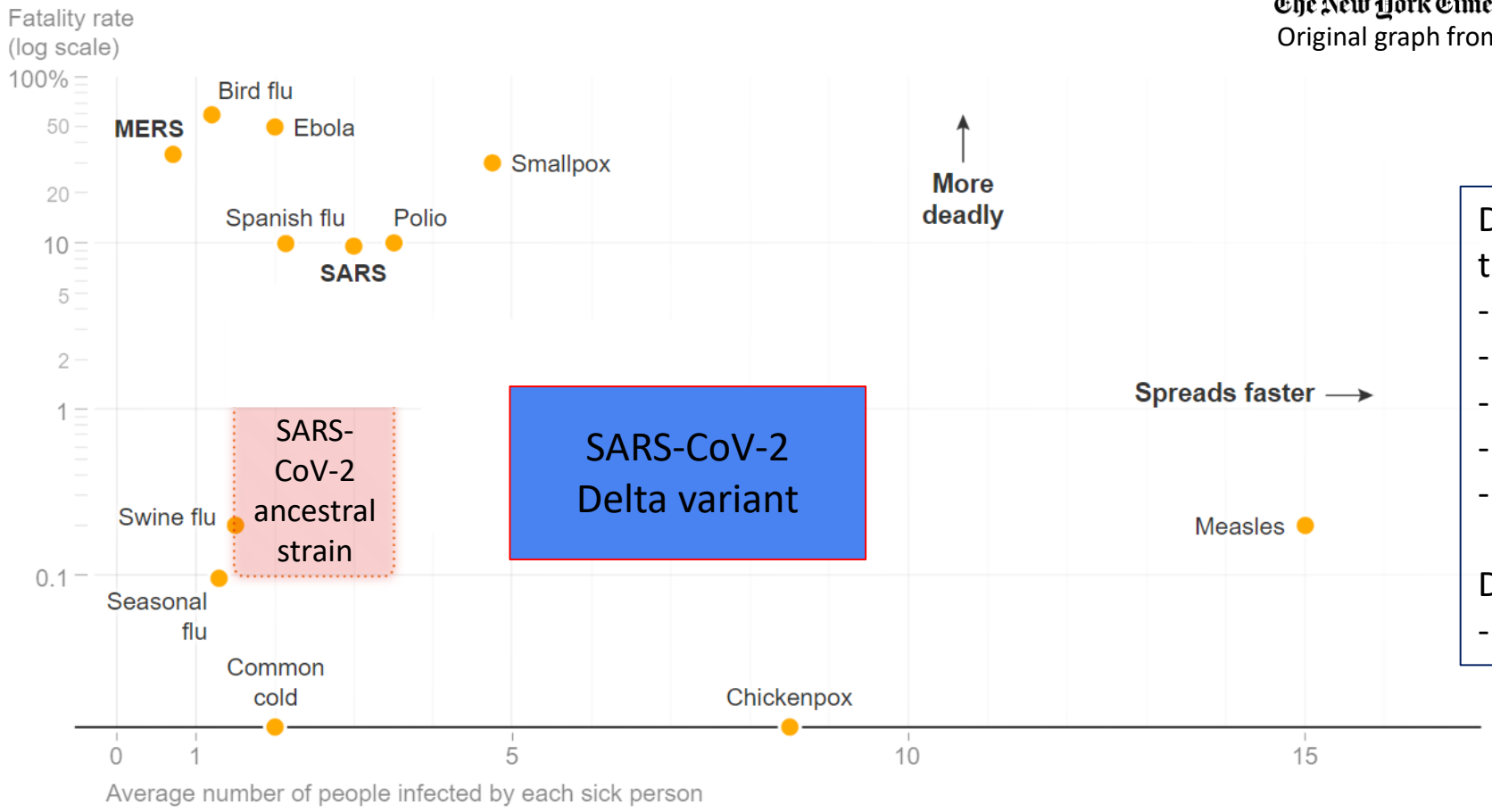


Communications challenges around VE and differential risk

- Vaccines more effective against hospitalization/death > illness > infection
  - Important to acknowledge lower VE against infection
- VE estimates represent an average for a group, rather than individual risk
  - Risk modified by age, immunocompromising conditions, etc.
  - Need to clarify messages around individual protection
- How do we communicate this differential risk to the public?
  - Comparisons to unvaccinated that are relatively stable
  - Personal stories
  - Examples from outbreaks

Delta variant

Transmission of Delta variant vs. ancestral strain and other infectious diseases



Delta variant is **more** transmissible than:
- MERS & SARS
- Ebola
- Common cold
- Seasonal flu & 1918 (“Spanish”) flu
- Smallpox

Delta variant is **as** transmissible as:
- Chicken Pox

Delta infections associated with higher viral load and duration of shedding: Published evidence

- India report of lower cycle threshold (Ct) values in Delta breakthrough cases in HCW (n=47, mean Ct 16.5) compared to non-Delta breakthrough cases (n=22, mean Ct 19); also larger cluster size with Delta breakthrough
- Delta infection associated with longer duration of Ct values ≤30 [median 18 days vs. 13 days for ancestral strains]
- Risk of reinfection with Delta may be higher [aOR 1.46 (CI 1.03-2.05)] compared to Alpha variant, but only if prior infection ≥180 days earlier

Micochova et al. doi: 10.21203/rs.3.rs-637724/v1
Ong et al. doi:10.2139/ssrn.3861566; PHE technical briefing 19:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1005517/Technical_Briefing_19.pdf

Delta variant vaccine breakthrough cases may be as transmissible as unvaccinated cases

- Breakthrough cases reported to national passive surveillance have lower Ct values by 3 cycles **(~10-fold increase in viral load) for Delta** (Ct=18, n=19) compared with Alpha (Ct=21, n=207) and other lineages (Ct=21, n=251)

- Barnstable County, MA, outbreak: **No difference in mean Ct values in vaccinated and unvaccinated** cases [median among vaccinated (n=80): 21.9; unvaccinated (n=65): 21.5]

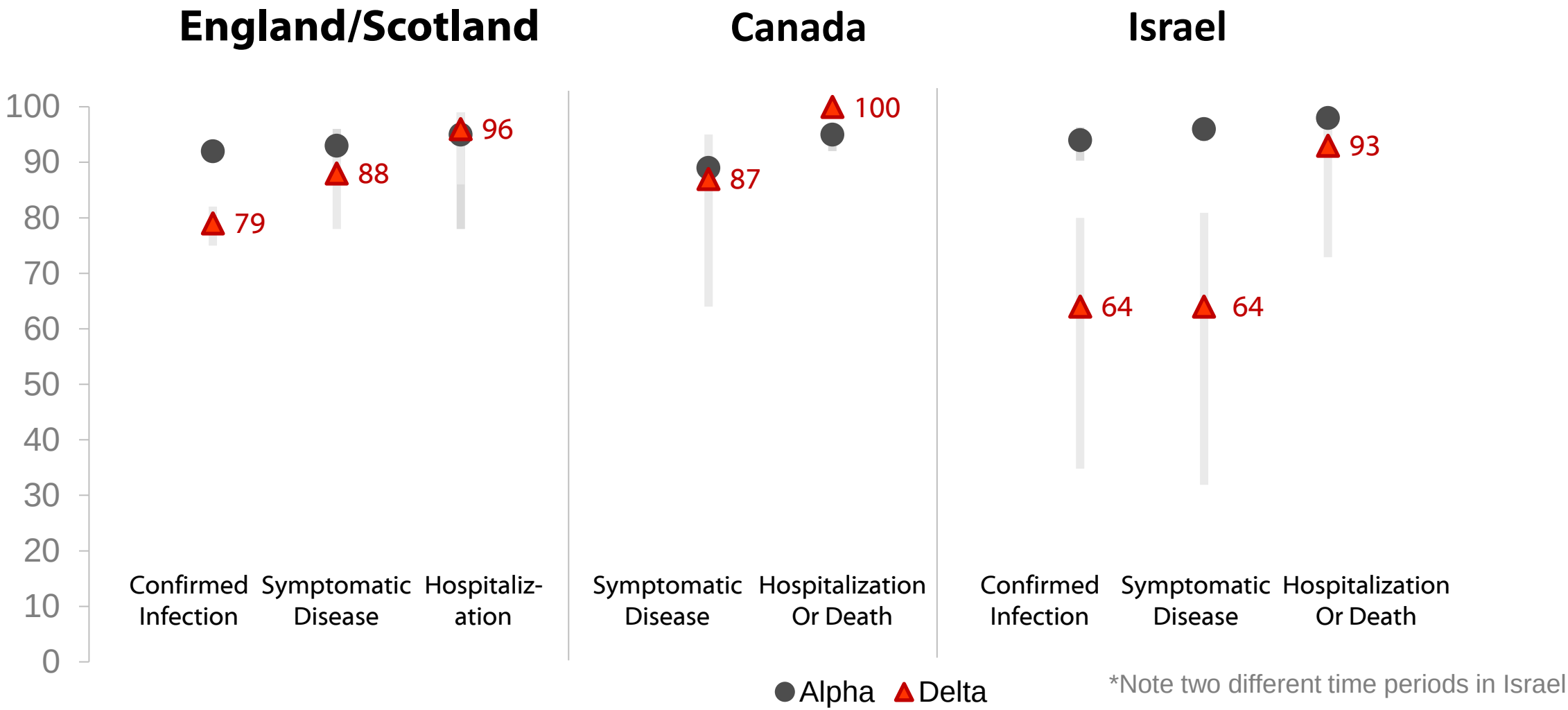
(CONFIDENTIAL – preliminary data, subject to change)

Delta variant may cause more severe disease than Alpha or ancestral strains: Published evidence

- Canada: Higher odds of hospitalization [aOR 2.20 (CI 1.93-2.53)], ICU admission [aOR 3.87 (CI 2.98-4.99)], and death [aOR 2.37 (CI 1.50-3.30)][1]
- Singapore: Higher odds of oxygen requirement, ICU admission, or death [aOR 4.90 (CI 1.43-30.78)] and pneumonia [aOR 1.88 (CI 0.95-3.76)][2]
- Scotland: Higher odds of hospitalization [HR 1.85 (CI 1.39-2.47)][3]

1. Fisman and Tuite, doi:10.1101/2021.07.05.21260050; 2. Ong et al. doi:10.2139/ssrn.3861566; 3. Sheikh et al. doi:10.1016/S0140-6736(21)01358-1

Pfizer 2-Dose Vaccine Effectiveness for Alpha vs. Delta



*Note two different time periods in Israel

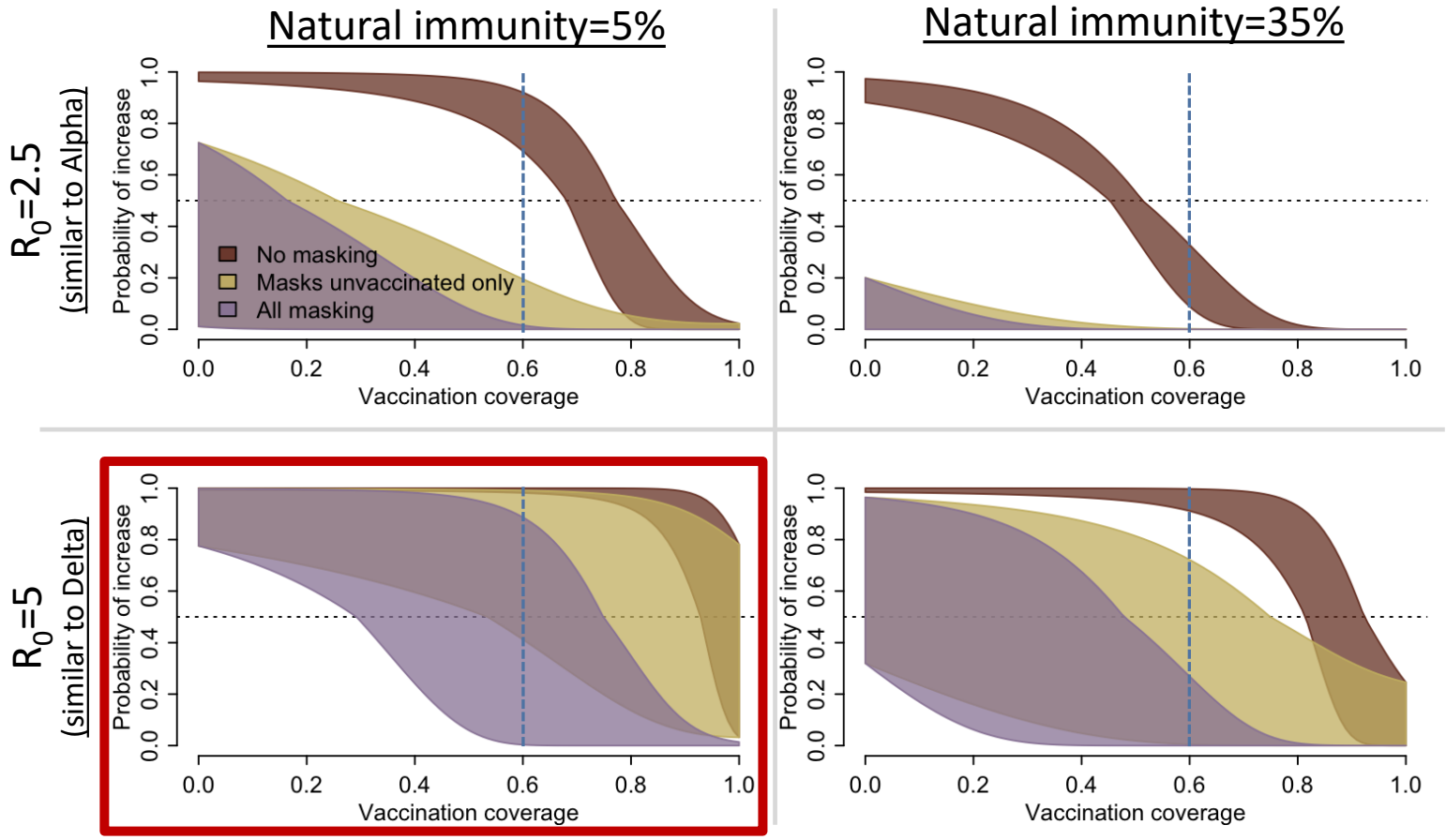
Sheikh et al. Lancet (2021): https://doi.org/10.1016/S0140-6736(21)01358-1; Lopez Bernal et al. medRxiv preprint; https://doi.org/10.1101/2021.05.22.21257658; Stowe et al. PHE preprint: https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266; Nasreen et al.medRxiv preprint: https://doi.org/10.1101/2021.06.28.21259420; https://www.gov.il/en/departments/news/06072021-04

Given increased transmissibility, lower VE, and current vaccine coverage, NPIs needed to reduce transmission of Delta variant

Reported incidence 50 cases per 100,000 per week

Model Assumptions:

- Vaccine effectiveness 75-85%
- 50% infections reported
- Masking:
  - Source control 40-60% effective
  - Personal protection 20-30% effective
- NO ADJUSTMENTS FOR OTHER INTERVENTIONS
  - e.g., no distancing, no isolation, no gathering restrictions

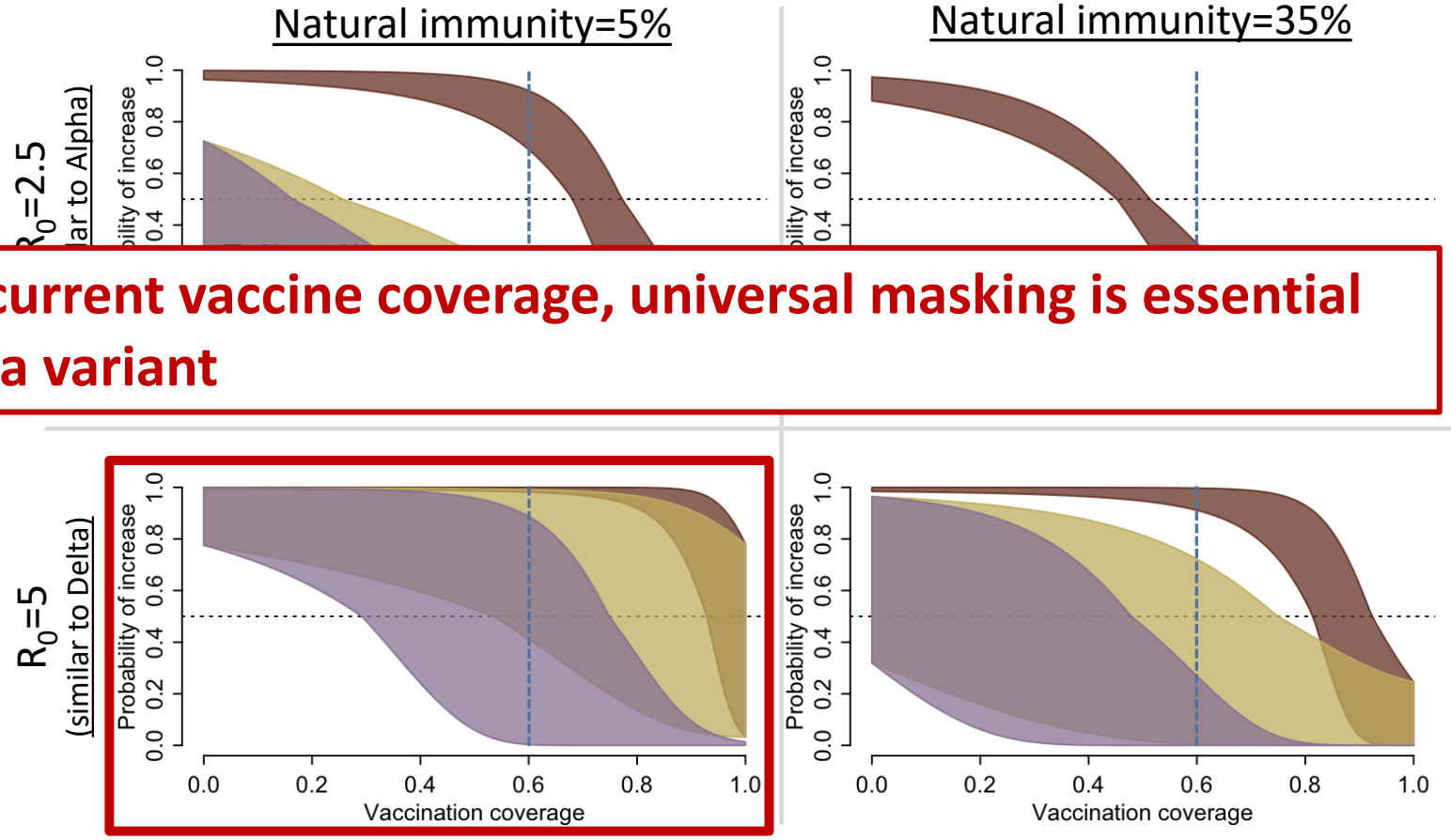


Given increased transmissibility, lower VE, and current vaccine coverage, NPIs needed to reduce transmission of Delta variant

Reported incidence 50 cases per 100,000 per week

Model Assumptions:

- Vaccine effectiveness 75-85%
- 50% infections reported



Given higher transmissibility and current vaccine coverage, universal masking is essential to reduce transmission of the Delta variant

- NO ADJUSTMENTS FOR OTHER INTERVENTIONS
  - e.g., no distancing, no isolation, no gathering restrictions

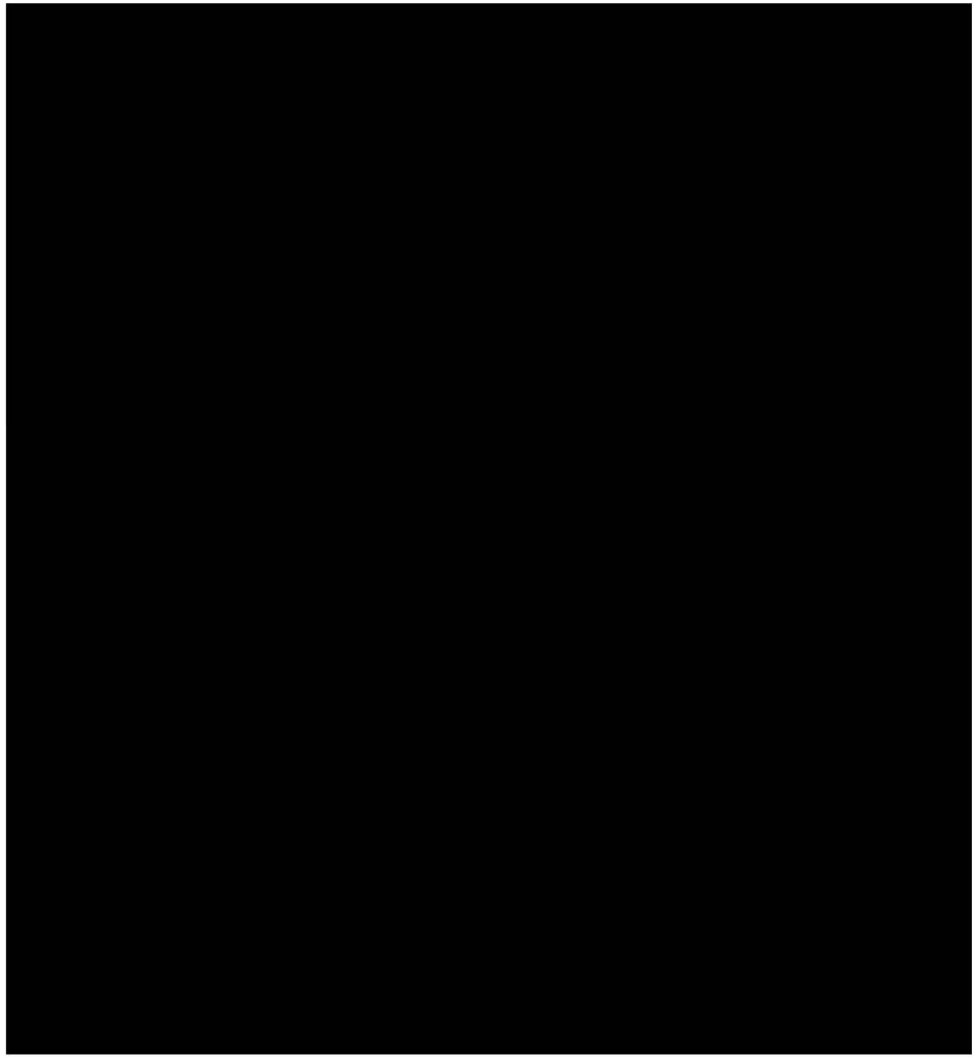
Summary

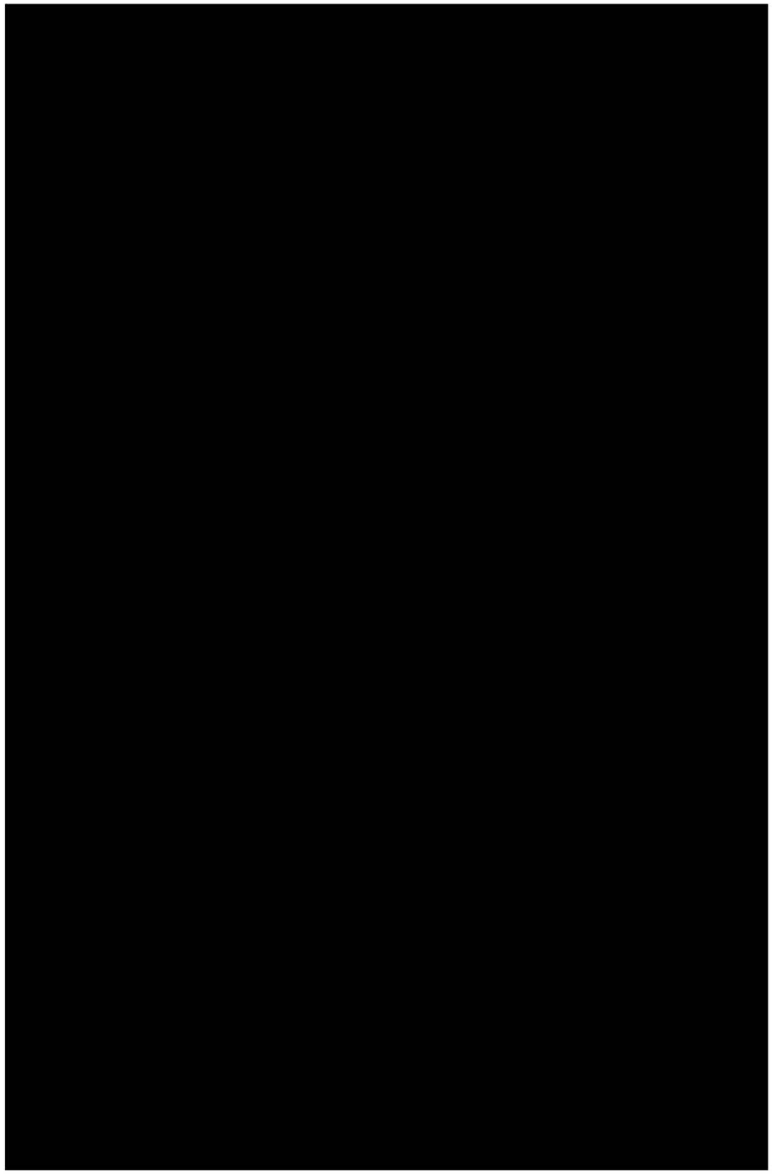
- Delta is different from previous strains
  - Highly contagious
  - Likely more severe
  - Breakthrough infections may be as transmissible as unvaccinated cases
- Vaccines prevent >90% of severe disease, but may be less effective at preventing infection or transmission
  - Therefore, more breakthrough and more community spread despite vaccination
- NPIs are essential to prevent continued spread with current vaccine coverage

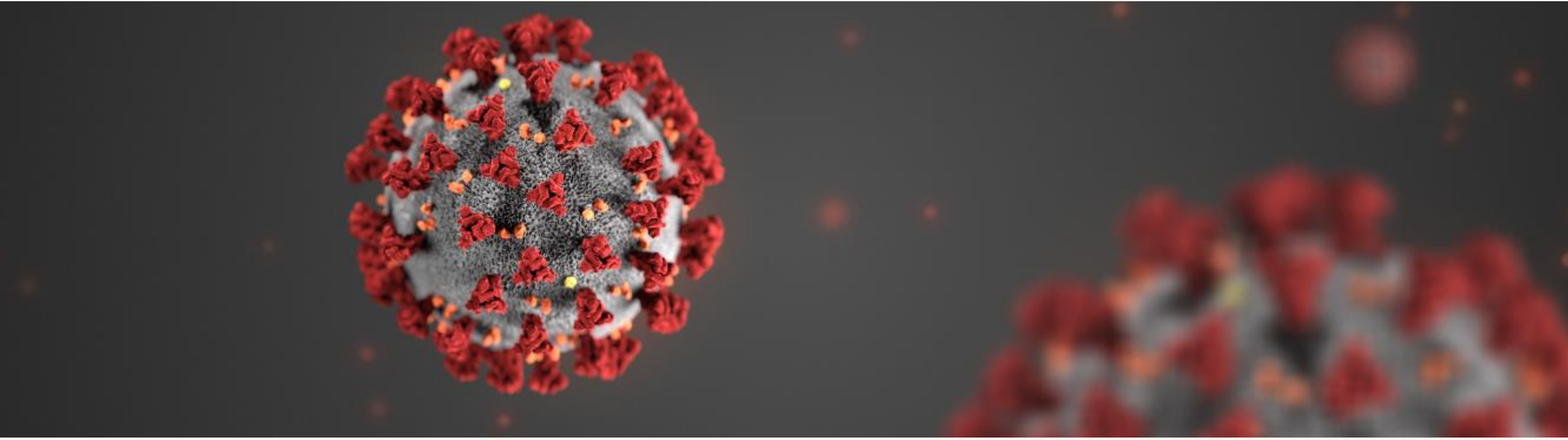
Next steps for CDC

- Communications
  - Acknowledge the war has changed
  - Improve public's understanding of breakthrough infections
  - Improve communications around individual risk among vaccinated
    - Risk of severe disease or death reduced **10-fold or greater** in vaccinated
    - Risk of infection reduced **3-fold** in vaccinated
- Prevention
  - Consider vaccine mandates for HCP to protect vulnerable populations
  - Universal masking for source control and prevention
  - Reconsider other community mitigation strategies

Acknowledgements







For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.