

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: Confirmed U.S. Deaths Pass 370,000

In the world as of January 11, 2021, 90,604,773 cases and 1,939,488 deaths have been confirmed. In the United States, there have been 22,463,467 cases, the most in the world followed in order by India, Brazil, Russia and the United Kingdom. China is now 81st in the world with a total of 96,882 reported cases. Deaths in the U.S. through January 11 have been estimated at 374,749.¹

From March 10 through January 5, there have been 141,303 confirmed cases of Covid-19 reported from Dallas County with 1,570 deaths, about 22% of these from long-term care facilities.² Sixty-eight percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men (63%) than women (37%) have died, and 46% of the hospitalized cases have occurred in the Hispanic population. As of 1/5/2021, deaths have been analyzed by race with 25% occurring in Whites (actual White population 29%), Hispanics 46% (population 41%), Blacks 25% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 12/5/20 being 21.6%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests and RSV antigen tests in specimens from the respiratory tract from 10/3 through 12/5/2020 have been negative. On 12/5/20, it was reported that there were 96 LTCF outbreaks which over the last 30 day period resulted in 928 cases including 364 staff members. There also were 26 outbreaks in congregate living facilities (homeless shelters, group homes and halfway houses) which over a 30 day period resulted in 166 cases.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 1/11/21)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 1/11/21

Feature Article

The Intersection between COVID-19 and HIV

Jeremy Chow, MD, Division of Infectious Diseases and Geographical Medicine

With the recent discovery of SARS-CoV-2 and its rapid growth into a pandemic, it has been established that older age, underlying conditions, and immunocompromise are associated with poorer outcomes. The scientific and medical communities are starting to learn how these principles apply to people with other immunocompromising conditions such as HIV, who may become infected with SARS-CoV-2. As there are approximately 1.2 million people in the US and 38 million people living with HIV (PWH) in the world, and since PWH are living longer, the effect of the COVID-19 pandemic on PWH has become a topic of great interest. This article will aim to summarize some of the research on the incidence and outcomes of COVID-19 in PWH, acknowledging that these studies have many limitations, and that information is rapidly changing.

Incidence

Overall, most of the studies that measure the incidence of COVID-19 among PWH suggest that PWH are not at increased risk of COVID-19, though this has differed based on the geographic location. Depending on the country, jurisdiction, or institution, findings may vary because of the respective policies and characteristics of that region's COVID-19 epidemic as well as the characteristics and behaviors of the PWH in that region.

In a review performed among 6,587 PWH who were diagnosed with COVID-19 across 23 studies from diverse geographic locations including the US, Brazil, Spain, Mexico, and South Korea, crude estimates were calculated and showed that PWH were diagnosed with COVID-19 more frequently than expected given the prevalence of HIV in each respective study catchment area.¹ Some of this increased risk may be explained by demographics.

In a large study done in NY state that merged HIV surveillance, COVID-19 laboratory, and hospitalization databases, PWH were more frequently diagnosed with COVID-19 than those without diagnosed HIV (RR 1.43, 95% CI: 1.38-1.48), but once sex, age, and region were accounted for, this disparity was no longer present.²

We also know that just as HIV has greatly affected racial minority communities, COVID-19 also has disproportionately affected these groups,³ which may explain why the incidence of COVID-19 among PWH may be high in the US. In contrast, two studies from Spain found a lower incidence of COVID-19 in PWH as compared to the Spanish general population,^{4,5} even after adjusting for age and sex.⁴

The limited current data suggest that HIV infection is not an independent risk factor for COVID-19, though more large population-based studies are needed to confirm this, especially as there may be variation based on country and context.

Outcomes

When considering the prognosis of PWH with COVID-19, several small case series early in the pandemic found that clinical outcomes did not differ significantly from those without HIV.⁶⁻¹³ More recently, larger studies have been published that provide more detailed and nuanced information.

Data from the Veterans Aging Cohort Study compared outcomes among patients diagnosed with COVID-19, of which 253 were mostly males with HIV who were matched to 504 HIV-negative participants. They found that there was no difference in intensive care unit admission, intubation, or death in those with or without HIV after adjusting for age, race/ethnicity, and sex.¹⁴

In contrast to these findings, a large study among public sector patients in South Africa found that HIV was associated with a doubling of COVID-19 mortality risk across all strata of viral loads and immunosuppression, even after adjusting for age, sex, location, and comorbidities.¹⁵

Another large population-based study in the United Kingdom also showed a markedly raised risk of COVID-19 death among PWH (HR 2.30, 95%CI: 1.55-3.41) even after adjustment for age, sex, race/ethnicity, and comorbidities, with this association even higher among black patients. These findings held true despite the high levels of antiretroviral therapy coverage and viral suppression in the UK.¹⁶

Finally, in perhaps the largest US-based study from the TriNETX multicenter research network, 50,167 patients with COVID-19 were identified, of which 404 had HIV. They found that PWH were more likely to need inpatient services (RR 1.83, 95%CI: 1.496-2.24), and their crude mortality was higher (RR 1.55, 95% CI: 1.01-2.39). However, after propensity score matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence, and sex, they found that there was no difference in mortality, though the difference in need for inpatient services remained.¹⁷ This suggests that differences in mortality are largely driven by these comorbidities and not the HIV itself.

A few studies have also sought to identify the association between COVID-19 outcomes and HIV severity markers (i.e. CD4 count and viral load), since these were not studied in prior studies. A multi-center COVID-19 and HIV registry study of 286 patients mostly from the US, found that a CD4 count <200 cells/mm³, in addition to older age, chronic lung disease, and hypertension, were associated with more severe outcomes (ICU admission, mechanical ventilation, and death), while the antiretroviral regimen and viral suppression were not.¹⁸

The New York State summarized above also found that the risk of hospitalization increased with disease progression from HIV stage 1 (CD4 $\geq$ 500) to Stage 3 (CD4 $<$ 200), as well as for those virally unsuppressed (aRR 1.54, 95%CI: 1.24-1.91).

The risk of incident COVID-19 among PWH and the prognosis among those with both COVID-19 and HIV are multifactorial and are dependent on location, context, and individual characteristics. Close attention should be given to the prevalence of COVID-19 in the communities each patient comes from as well as the patient's individual comorbidities and degree of immunosuppression, since these may affect their risk for poorer COVID-19 outcomes.

References:

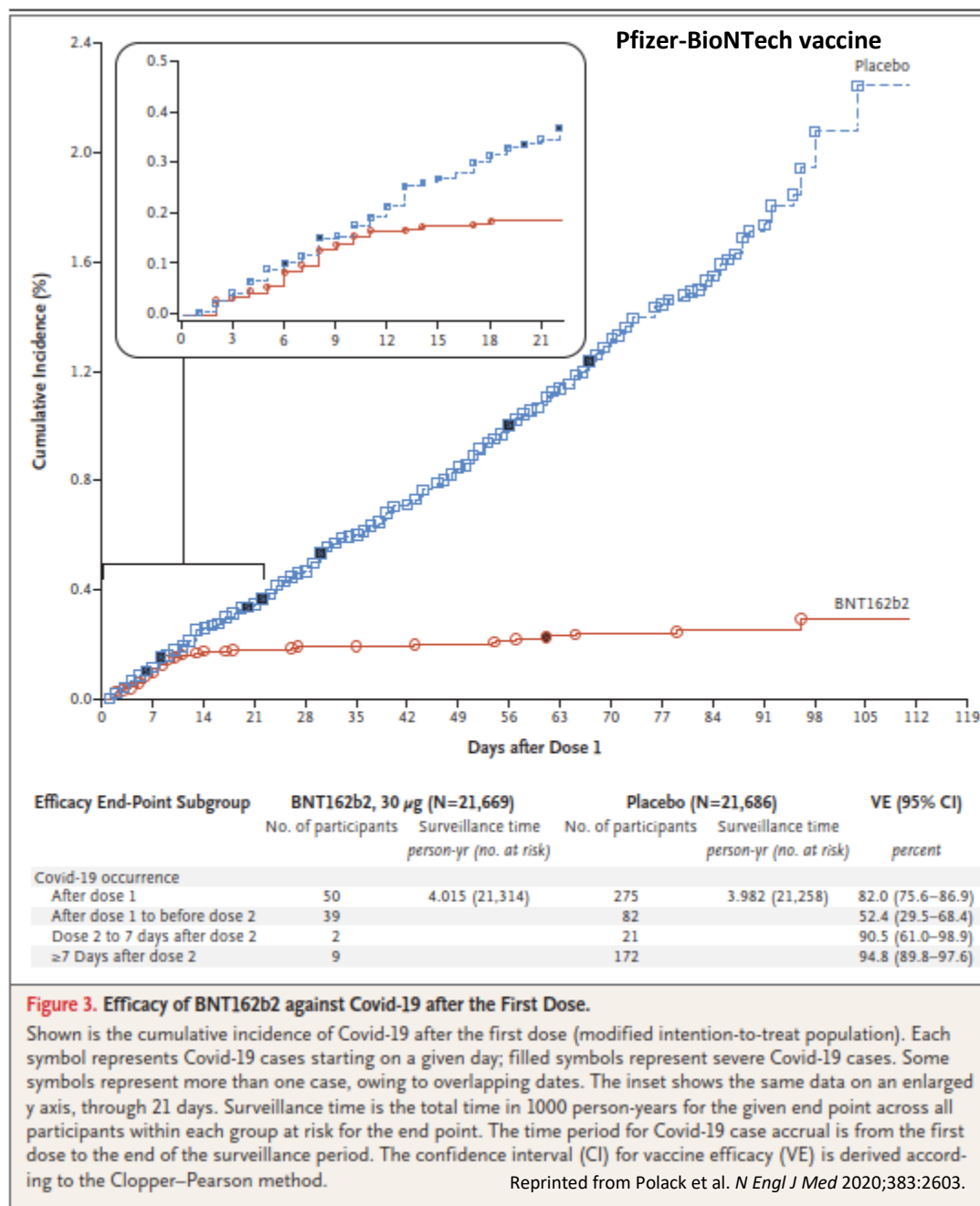
1. Johnston R. The first 6 months of HIV-SARS-CoV-2 coinfection: outcomes for 6947 individuals. *Curr Opin HIV AIDS* 2020. DOI: 10.1097/COH. DOI: 10.1097/COH.0000000000000654
2. Tesoriero JM, Swain CE, Pierce JL, et al. Elevated COVID-19 outcomes among persons living with diagnosed HIV infection in New York State: Results from a population-level match of HIV, COVID-19, and hospitalization databases. *medRxiv* 2020. DOI: 10.1101/2020.11.04.20226118
3. Meyerowitz EA, Kim AY, Ard KL, et al. Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV. *AIDS* 2020;34:1781-7. DOI: 10.1097/QAD.0000000000002607.
4. Del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy : A Cohort Study. *Ann Intern Med* 2020;173:536-41. DOI: 10.7326/M20-3689
5. Inciarte A, Gonzalez-Cordon A, Rojas J, et al. Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-center, prospective observational study. *AIDS* 2020;34:1775-80. DOI: 10.1097/QAD.0000000000002643
6. Byrd KM, Beckwith CG, Garland JM, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. *J Int AIDS Soc* 2020;23:e25573. DOI: 10.1002/jia2.25573
7. Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of HIV patients with coronavirus disease. 2019. *Clin Infect Dis* 2020. DOI: 10.1093/cid/ciaa579
8. Harter G, Spinner CD, Roeder J, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection* 2020;48:681-6. DOI: 10.1007/s15010-020-01438-z
9. Karmen-Tuohy S, Carlucci PM, Zervou FN, et al. Outcomes Among HIV-Positive Patients Hospitalized With COVID-19. *J Acquir Immune Defic Syndr* 2020;85:6-10. DOI: 10.1097/QAI.0000000000002423
10. Shalev N, Scherer M, LaSota ED, et al. Clinical Characteristics and Outcomes in People Living With Human Immunodeficiency Virus Hospitalized for Coronavirus Disease. 2019. *Clin Infect Dis* 2020;71:2294-7. DOI: 10.1093/cid/ciaa635
11. Sigel K, Swartz T, Golden E, et al. Covid-19 and people living with HIV infection: outcomes for hospitalized patients in New York City. *Clin Infect Dis* 2020. DOI: 10.1093/cid/ciaa880
12. Stoeckle K, Johnston CD, Jannat-Khah DP, et al. COVID-19 in Hospitalized Adults With HIV. *Open Forum Infect Dis* 2020;7:ofaa327.
13. Vizcarra P, Perez-Elias MJ, Quereda C, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV* 2020;7:e554-e64. DOI: 10.1016/S2352-3018(20)30164-8
14. Park LS, Rentsch CT, Sigel K, et al. COVID-19 in the largest US HIV cohort. *AIDS* 2020: 23rd International AIDS Conference. Virtual2020. https://www.natap.org/2020/IAC/IAC_115.htm
15. Davies MA. HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa. *medRxiv* 2020. DOI: 10.1101/2020.07.02.20145185
16. Krishnan Bhaskaran CTR, Brian MacKenna, Anna Schultz, Amir Mehrkar, Chris Bates, Rosalind M Eggo, Caroline E Morton, Seb Bacon, Peter Inglesby, Ian J Douglas, Alex J Walker, Helen I McDonald, Jonathan Cockburn, Elizabeth J Williamson, David Evans, Harriet J Forbes, Helen J Curtis, William Hulme, John Parry, Frank Hester, Sam Harper, Stephen JW Evans, Liam Smeeth, Ben Goldacre. HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *medRxiv* 2020. DOI: 10.1101/2020.08.07.20169490
17. Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. *AIDS* 2020;34:F3-F8. DOI: 10.1097/QAD.0000000000002666
18. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, Comorbidities, and Outcomes in a Multicenter Registry of Patients with HIV and Coronavirus Disease-19. *Clin Infect Dis* 2020. DOI: 10.1093/cid/ciaa1339

When Does Clinical Protection from Covid-19 Begin after mRNA Vaccination?

The interval between each vaccination dose and the onset and completeness of immunity to clinical Covid-19 illness is an important issue that has been addressed in reports of the Phase 3 clinical trials of the two mRNA vaccines.^{1,2} The figure on this page plots the cumulative occurrence of Covid-19 clinical cases in the 43,548 volunteer recipients of the **Pfizer-BioNTech mRNA vaccine** (red) or placebo (blue). The two curves diverge dramatically at the twelfth day after the first dose.¹ Given a median of 5 days incubation period from acquisition of infection to illness, immunity to acquisition of infection appears to begin at approximately 7 days after the first dose. At this point, vaccine efficacy compared to placebo is 82% (95% CI 76%-87%). From day 13 to day 28

(7 days after the second dose), only 6 clinical cases occurred in the vaccinated, and from day 28, when the immunity boost from the second dose is expected, for the remaining 90 days of the trial, only 9 more infections occurred.

After the first dose, only 1 case of severe disease occurred in the vaccinated group, compared with 9 in the placebo group (black markers in the figure). This apparent protection from severe disease begins to counter theoretical concerns over disease enhancement by the vaccine, as has occurred in a rare vaccine such as that for dengue.



The Phase 3 clinical trial of the **Moderna vaccine** in 30,000 volunteers found a highly similar time course as indicated in the figure on this page.² The two curves diverge dramatically before the fourteenth day after the first dose, when by protocol all subjects were checked. Given a median of 5 days incubation period, immunity to

acquisition of infection from this vaccine appears to begin at approximately 7-9 days after the first dose. At this point, vaccine efficacy compared to placebo appeared to be even higher than that for the Pfizer vaccine, although the level could not be calculated from the data given. From 14 days after the first dose to the second dose, only 2 clinical infections were recognized compared with 54 in the placebo group, and thereafter until the end of the trial only 12 were, compared with 204 in the placebo group, giving a total vaccine efficacy of 94% (95% CI 89% to 97%).

After the first dose, no cases of severe disease occurred in the vaccinated group, compared with 30, including one death, in the placebo group. This further supports no vaccine-mediated disease enhancement.

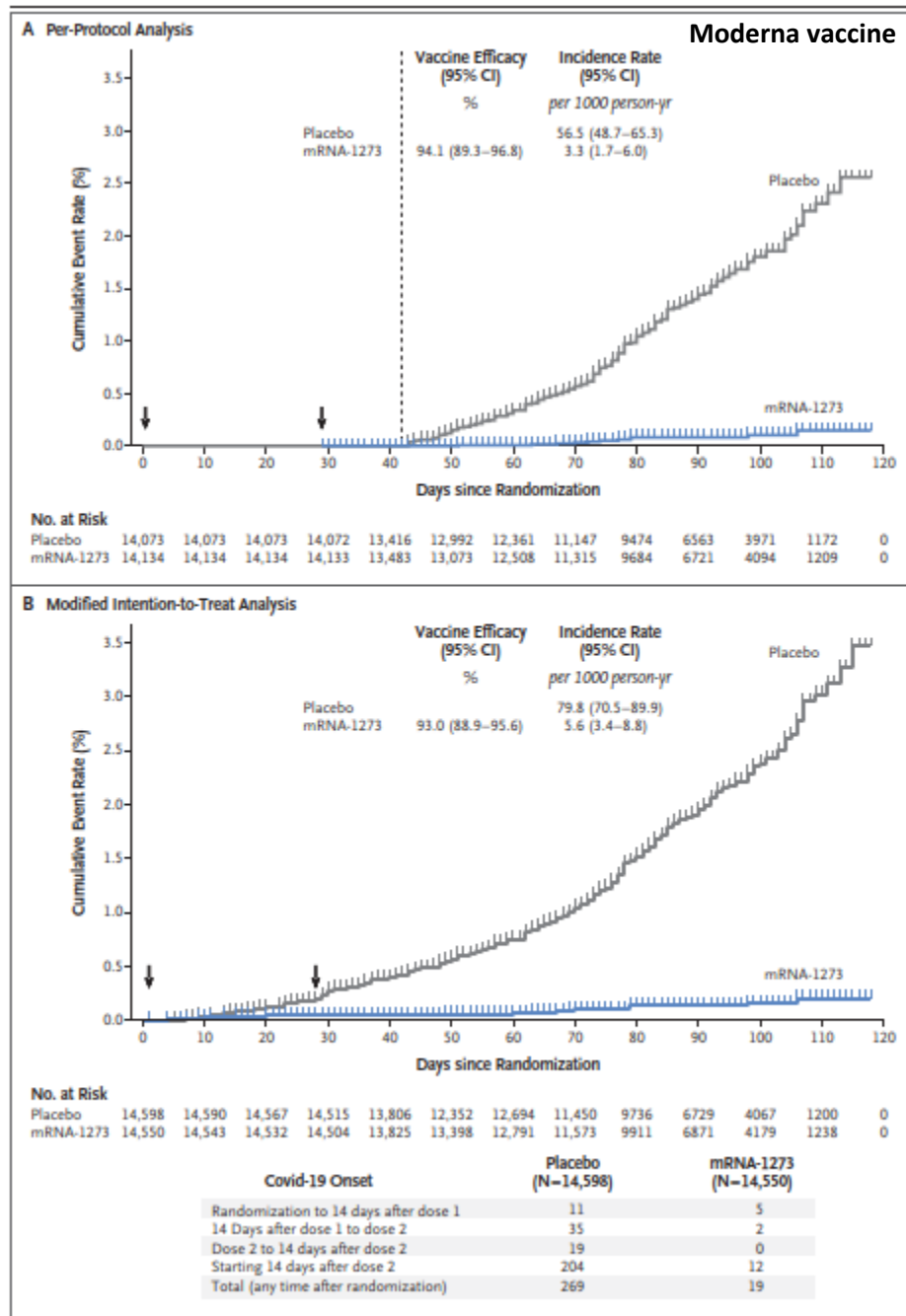


Figure 3. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19.

Shown is the cumulative incidence of Covid-19 events in the primary analysis based on adjudicated assessment starting 14 days after the second vaccination in the per-protocol population (Panel A) and after randomization in the modified intention-to-treat population (Panel B) (see the Supplementary Appendix). The dotted line in Panel A indicates day 42 (14 days after vaccination 2), when the per-protocol follow-up began, and arrows in both panels indicate days 1 and 29, when injections were administered. Tick marks indicate censored data. Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA vs. placebo), and the 95% confidence interval was estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with treatment group as a covariate, with adjustment for stratification factor. Incidence was defined as the number of events divided by number of participants at risk and was adjusted by person-years. Symptomatic Covid-19 case accrual for placebo and vaccine in the modified intention-to-treat population is displayed (does not include asymptomatic cases of SARS-CoV-2 detected at the day 29 by nasopharyngeal swab). Reprinted from Baden et al. *N Engl J Med* 2020 online.

Although neither trial was designed to assess efficacy after the first dose alone, the evidence from both trials supports a high degree of protection by 7-9 days after the first dose, although some caution in interpretation is indicated by wide confidence intervals due to small numbers of infections. The rationale for a second dose appears to be to boost effectiveness even further and to stimulate a higher antibody and T cell response that might prolong the duration of immunity.

In weighing the size of the boost in immunity from the second dose against the urgency to accelerate population coverage, the incoming administration is preparing to release all vaccine stores to the states immediately for first shots rather than holding back the stocks needed for second shots. Presumably second shots will be easier to provide as vaccine manufacture continually accelerates. At present, it is not clear what effect delaying the second shot will have on efficacy and longevity of the response.

References:

1. Polack et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine [Pfizer-BioNTech]. *N Engl J Med* 2020; 383(27):2603-2615. DOI: 10.1056/NEJMoa2034577
2. Baden et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine [Moderna]. *N Engl J Med* 2020; published online 30 Dec. DOI: 10.1056/NEJMoa2035389

Epi Corner

We Need to Tell New Vaccinees Not to Give Up Their Masks Yet

A vital question not addressed by the vaccine trials reported to date is the degree to which one or two doses of the vaccines prevent vaccinees from contracting asymptomatic infection which they can unknowingly spread to others. Without that information, we must assume that it is possible, maybe even common, and constitutes a serious threat to the close contacts of the vaccinated. For example, influenza vaccination confers what is called “sterilizing immunity” which prevents asymptomatic infection and transmission from vaccinees; whereas, the formalin-inactivated polio vaccination did not.

Certainly, the two mRNA vaccines are so effective in preventing clinical disease that they might prevent this problem, but if they do not, our vigorous and well-organized vaccination campaigning could have the unintended consequence of harming the loved ones of the vaccinees we are protecting.

While this risk has been emphasized in clinical and public health circles, the message clearly has not gotten out to the public. Stories abound of healthcare workers and older adults eager to get their shots so they can go on that cruise or reunite with their extended families without that bothersome mask. Until ongoing studies clarify this issue, it is urgent that effective public health messaging be delivered to new vaccinees to inform and convince them to continue masking and distancing until the potential risk has been studied.

Clearly the most impactful and cost-efficient setting for delivering this message is right as people are being vaccinated. Every vaccination station should be provided with an attractive sign that delivers the message, and the worker delivering the vaccine should point to the sign and emphasize the advice (see figure on the next page). This most effective messaging should be supplemented by public reminders such as public service announcements, billboards and media editorials. If future research shows that the vaccines prevent asymptomatic infection and transmission, we can call off the campaign, but until then, we should deliver a potentially life-saving message along with the life-saving vaccine.

References:

1. CDC. What to expect after getting a COVID-19 vaccine. January 11, 2021. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/expect/after.html>
2. Peiris M, Leung GM. What can we expect from first-generation COVID-19 vaccines? *Lancet* 2020; 396:1467-1469



From the Editors

The editors thank Dr. Chow for his feature article on Covid-19 and HIV.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.