



COVID-19 Action Newsletter

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The Situation: Confirmed U.S. Deaths Pass 280,000

In the world as of December 7, 2020, 67,316,936 cases and 1,539,965 deaths have been confirmed. In the United States, there have been 14,793,047 cases, the most in the world followed in order by India, Brazil, Russia and France. China is now 71st in the world with 93,655 cases. Deaths in the U.S. through December 7, 2020 have been estimated at 282,522.¹

From March 10 through December 6, 2020 there have been 134,677 confirmed cases of Covid-19 reported from Dallas County with 1,234 deaths, about 25% 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 than women have died, and 52% of the hospitalized cases have occurred in the Hispanic population. As of 12/4, 1,057 deaths have been analyzed by race with 24% occurring in Whites (actual White population 29%), Hispanics 47% (population 41%), Blacks 25% (population 25%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 11/28 being 22.3%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests in specimens from the respiratory tract from 8/1 through 11/28 have been negative except for 2 cases (0.6%) being positive during the week ending 10/24. Ninety-seven active long-term care facility outbreaks are presently being investigated and managed. In addition, there are 22 outbreaks of Covid-19 in congregate-living facilities (homeless shelters, group homes and halfway homes) that have been reported with 168 cases in the last 30 days. One of these facilities had 87 confirmed Covid-19 cases.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 12/7/20)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 12/6/20

Feature Article

An Overview of COVID-19 Vaccines

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The rapid development and testing of COVID-19 vaccines has been a priority since the onset of the pandemic and has moved at unprecedented speed. At present, there are over 200 vaccine candidates in the pipeline with over 60 that have reached Phase, 1,2 or 3 clinical trials. These vaccine candidates utilize a variety of platforms including whole virus (inactivated or live), protein subunit, viral vector and nucleic acid based (mRNA and DNA). The acceleration of these candidates through clinical trials has been aided by prior knowledge of Spike protein (from SARS-CoV-1) as potential antigenic target, early availability of the genetic sequence for SARS-CoV-2 in January 2020, and the huge public and private financial investment that have allowed vaccine manufacturers to “assume success ahead” and invest in subsequent phases of development without waiting for preliminary results. This minimizes any potential pauses in the clinical trials process. Alongside this, a significant financial

risk has been undertaken to begin “manufacturing in parallel” of vaccine candidates prior to FDA approval so that there is limited delay in distribution should a COVID-19 vaccine candidate be approved.¹

Data from Phase 1 and 2 trials of several COVID-19 vaccine candidates have been published.²⁻⁴ Vaccine candidates using different platforms have shown the ability to generate good neutralizing antibody responses to Spike protein (comparable or exceeding those in convalescent sera from infected patients). T cell responses have also been demonstrated, and importantly, these responses have also been seen in those over 65 years of age. It appears that the majority of vaccine candidates will require a 2nd dose to elicit sufficient immune responses. It is important to re-iterate that there is no proven immune correlate of protection for SARS-CoV-2 and so, while immunogenicity will be monitored during Phase 3 trials, the primary efficacy endpoint remains ability of the vaccine to protect from symptomatic, virologically confirmed (PCR positive) disease. Phase 1/2 studies have also demonstrated vaccine candidates to be well tolerated with expected local and systemic minor adverse events (e.g., pain at injection site, fatigue) but no major safety concerns based on the observations thus far.

Candidate	Manufacturer	Type	Characteristics	Target Enrollment	Status
mRNA-1273	Moderna TX, Inc	mRNA	2 doses (0, 28 days) IM administration 18-55, +65 years	30,000	Enrollment complete EUA application forthcoming
mRNA-BNT162b2	BioNTech and Pfizer, Inc	mRNA	2 doses (0,21 days) IM administration 18-85 years	44,000	Enrollment almost complete Interim results Nov 5 EUA application submitted
AZD1222	Univ of Oxford and AstraZeneca	Adenovirus vector (Chimp)	2 doses, (0,28 days) IM administration +18 years	30,000	Clinical hold in Oct Enrolling Results end of year
Ad26 COVS1	Janssen Pharmaceutical Companies	Adenoviral vector (26)	1 dose IM administration + 18 years	60,000	Clinical hold in Oct Enrolling Results end of year
SARS-CoV-2 rS	Novavax	Recomb Protein Subunit with Matrix M	2 doses (0,21 days) IM administration 18-84 years	30,000	Phase 3 starting USA end of November Interim data from Ph 3 from UK expected 2021

Table 1 Phase 3 COVID-19 vaccine candidates with trial sites in the USA

Table 1 lists the current Phase 3 COVID-19 vaccine candidates in the USA that have either completed enrollment or still enrolling. In the last few weeks, there have been several press releases regarding Phase 3 trial COVID-19 efficacy vaccine results. Two mRNA vaccine candidates, mRNA-1273 by Moderna and BNT162b2 by Pfizer, have reported Phase 3 primary vaccine efficacy endpoints 94% and 95%, respectively. More recently the University of Oxford and AstraZeneca reported an average efficacy of 70% with their Chimp Adenoviral Vector vaccine AZD1222 based on data combined from two Phase 3 trials conducted in the UK and Brazil. These efficacy results are event-driven analyses that are analyzed by an independent board when the trials achieve pre-specified thresholds of COVID-19 cases. Following this, the distribution of cases between the placebo and vaccine group is analyzed to calculate vaccine efficacy (protection from symptomatic, PCR-confirmed COVID-19). Reassuringly, all trials have also reported no major safety concerns. Two Phase 3 clinical trials (Astra Zeneca and Janssen Pharmaceutical Companies) using Adenoviral vector vaccines have had clinical holds related to illnesses in two single participants, but after further investigation of the events and independent review, their clinical trials have resumed. Such events are an expected part of the vaccine trials process, and these pauses should be interpreted as a testament to the integrity and safety of the process of vaccine development.

As we approach winter with the escalating COVID-19 cases and deaths, these preliminary results are encouraging news since all reports are above the FDA recommended vaccine efficacy threshold of 50%. These results are also a validation of the approach for the mRNA vaccine format (which has never been FDA licensed before) and use of Spike protein as an antigenic target. At the time of writing, several questions remain

unanswered regarding long-term durability of vaccine-induced protection, impact in different subgroups, and prevention of asymptomatic infection. In addition, these trials are not designed to look at impact on transmission, and thus the importance of social distancing, use of mask and washing hands as preventative measures must continue to be emphasized even after people are immunized until the pandemic ends.

Pfizer has submitted an Emergency Use Authorization (EUA) for their vaccine candidate and Moderna will plan to submit an EUA this week. The FDA standard for administration of an EUA is that it must be effective in the prevention or treatment of COVID-19 and the risk/benefit ratio must be favorable. This process requires very careful consideration because, unlike COVID-19 therapeutics that may be given to sick, hospitalized patients potentially at risk of death, vaccines are administered to people who are otherwise healthy.

Even if an EUA is granted for one or more vaccine candidates, this does not spell the end for the COVID-19 vaccine race. Current trial participants will continue to be monitored for the duration of the trials (often up to 2 years), with close monitoring for potential vaccine-enhanced disease. Vaccine manufacturers are still expected to submit a full Biologics License Application even if an EUA is granted. It is essential that other trials continue to completion and are successful, as several vaccine candidates will be needed to meet the global need. Several months of national and state planning have occurred with regards to the distribution of a potential vaccine including logistics and cold chain supply and storage, particularly important for the mRNA vaccines that require storage at sub-zero temperatures, potentially as low as minus 75 degrees Celsius. Lastly the adage of “vaccines don’t save lives, vaccination saves lives” remains true as ever for COVID-19. An increasing sentiment of vaccine hesitancy, particularly marked in racial/ethnic minorities, has been reported.⁵ This may yet be the biggest obstacle to the COVID-19 vaccination strategy. Transparency, trust, and communication to the public will be essential in the coming months to allow COVID-19 vaccination to become a successful adjunctive measure in curbing the pandemic.

References

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Vaccine Update

Status of the First Vaccines as of December 7

Since this feature article was finalized, the vaccine companies have released the first numerical results of their Phase III trials. The **BioNTech-Pfizer** mRNA vaccine was evaluated in 43,661 volunteers, half over 65. Of the 170 Covid-19 symptomatic cases documented, 162 occurred in the placebo group and 8 in the vaccine group, for an efficacy of 95%. Of the 30,000 volunteers studied in the **Moderna** Phase III trial, there were 196 cases, 184 in the placebo group and 12 in the vaccine group, for an efficacy of 94%. The efficacy rates for both vaccines were consistent across age, sex and racial/ethnic subgroups. Moderna reported that no severe or fatal cases occurred in their vaccine group. Neither study identified any severe adverse effects from their vaccines, and minor reactions, such as pain and redness at the vaccine site, fatigue, fever, headache, and myalgias, commonly followed both. FDA is expected to issue EUDs to BioNTech-Pfizer a week ahead of the Moderna vaccine. This

time advantage occurred largely because the BioNTech-Pfizer vaccine's 2 doses are given 3 weeks apart, while Moderna's are given 4 weeks apart.

Since the government's Operation Warp Speed spent billions of dollars for manufacture of the leading candidate vaccines to be started months before the Phase III trials were completed, the companies will be rolling out millions of doses of their vaccines as soon as they are issued EUAs by the FDA. Pfizer intends to release 50 million doses by the end of December and 1.3 billion doses in 2021; whereas, Moderna intends to release 20 million doses in December and an undetermined number over 500 million doses in 2021. The BioNTech-Pfizer vaccine remains stable below -60° (dry ice) for 6 months, at refrigerator temperature for 5 days, and at room temperature for 2 minutes. The Moderna vaccine remains stable at -20°C (home freezer) for 6 months, at refrigerator temperature for 30 days, and at room temperature for 12 hours.

The **Oxford-AstraZeneca** vaccine, which uses an adenoviral vector to deliver spike protein DNA, was approved last week by the UK Government, some say prematurely, and will begin administration in the UK this week. Its Phase III trial studied only 11,000 volunteers in U.S. and Brazil. Due to a calculation error, the first group of subjects received only half the amount of vaccine in the first dose and the full amount in the second dose; the rest of the subjects received the full amount in both doses. Counterintuitively, the efficacy was 90% in the first group and 62% in the second. Since both results, as well as the average of 70%, exceeded the 50% level required for regulatory approval, the vaccine was approved in Britain. The company is planning a second Phase III trial to test whether the superior efficacy of the mistaken dosage schedule holds up. AstraZeneca plans to produce 3 billion doses in 2021. Advantages that make this vaccine preferable for developing countries include its lower cost (\$3 to \$4 per dose compared with \$15 to \$25 per dose for the Moderna and BioNTech-Pfizer vaccines) and its long shelf life of 6 months at refrigerator temperature.

Johnson and Johnson's vaccine unit **Janssen Pharmaceutical Companies**, in collaboration with vaccine scientists at Beth Israel Deaconess Medical Center/Harvard Medical School in Boston, and the Biomedical Advanced Research and Development Authority (BARDA) in DHHS, developed 7 vaccines from different segments of the SARS-CoV-2 spike protein RNA sequence and tested them in primates. They then brought the most immunogenic vaccine to human trials and are nearing completion of two parallel Phase III clinical trials of 30,000 volunteers each: the ENSEMBLE trial testing a single dose found to be highly immunogenic in primates and ENSEMBLE2 testing two doses 4 weeks apart found to be 10 times more immunogenic. If the one-shot dose appears adequate in the Phase III human trial, it will have an important logistical advantage in developing countries. These vaccines use Janssen's AdVac® adenoviral delivery technology that has proved safe and effective in their Ebola vaccine, now in field use in Africa, as well as in their Zika, RSV and HIV vaccine candidates, which are in Phase II and III trials. If successful, the company's factories worldwide intend to produce over 1 billion doses of both the single-dose and double-dose vaccines in 2021, half pledged to developing countries. These vaccines will remain stable at home freezer temperature for up to 2 years and at refrigerator temperature for 3 months.

Texas is to receive 1.4 million doses of the BioNTech-Pfizer vaccine, which will be divided among the 254 counties. Pfizer's highly developed distribution system will ship vaccine directly to institutions and clinics that have signed up to be distribution sites. The first vaccine doses are expected to be received during the week of December 14. Through the end of December and into January, while vaccine is in short supply, it will be administered first to healthcare workers caring for Covid-19 patients as well as residents and staff of nursing homes and other long-term-care facilities. Later supplies, including some of the Moderna vaccine, will be distributed according to priorities set by county governments considering the guidelines from CDC and the state government.

Editorial Update: As of December 18, the BioNTech-Pfizer vaccine has received an EUA and is being distributed, and the Moderna vaccine has been approved by the FDA advisory committee and is expected to receive an EUA within days.

From the Editors

The editors thank Dr. Arasaratnam for his feature article on Covid-19 vaccines.

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.