It is expected that EMS clinicians, other frontline healthcare professionals from hospitals and long-term care facilities, and residents of long-term care facilities will be among the first groups of individuals to be offered the COVID-19 vaccine. The timing of this and the initial number of doses Maine will receive remains uncertain. In anticipation of vaccine release, Maine EMS and the Medical Direction and Practices Board (MDPB) are preparing this reference guide with included talking points in an effort to share the most contemporary vaccine evidence available. Ultimately it is your decision whether you are vaccinated against COVID-19. Maine EMS and the MDPB hope this empowers you to make a meaningful decision regarding vaccination.

Please note that this Reference Guide is not intended to supplant the Maine EMS document "*Maine Vaccination Campaign Plan for Public Safety Professionals*." That document is intended to discuss the logistics and operations of vaccine implementation and can be found on the Maine EMS Website, under "Coronavirus (COVID-19) EMS Resource Page". Instead, this document is intended to describe the science and evidence surrounding the COVID-19 vaccine so that you may make an educated decision in regard to vaccination.

This bulletin is divided into specific topics, including:

1. General information,
2. Information regarding the process of developing these vaccines,
3. Information regarding the technology of the vaccines,
4. Safety information, and
5. Efficacy information.

General Information

CDC: Common COVID-19 Vaccination Facts

COVID-19 Vaccines will NOT give you COVID-19[1]

- None of the COVID-19 vaccines currently in development in the United States use the live virus that causes COVID-19.
- The goal for each of the vaccines is to "teach" our immune system how to recognize and fight the virus that causes COVID-19. Sometimes this process can cause symptoms, such as fever, body aches, headaches, and fatigue as well as local reactions at the injection site.
- **These symptoms are normal** and are a sign that the body is building immunity.

[1] From the website: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccine-benefits/facts.html. Accessed on December 2, 2020

COVID-19 Vaccines will NOT cause you to test positive on COVID-19 viral PCR tests [1,2,3]

- The goal of vaccination is for your body to develop an immune response.
- This immune response will not cause you to test positive when tested using PCR tests.
- Once your body develops an immune response, there is a possibility you may test positive on some antibody tests. Antibody tests indicate you had a **previous exposure to the virus, or parts of the virus (i.e. the spike protein),** and that you may have some level of protection against the virus. Experts are currently looking at how COVID-19 vaccination may affect antibody testing results.

People who have gotten sick with COVID-19 may still benefit from getting vaccinated. [1]

- **At this time, the duration of the immune response after infection is uncertain**. The immunity someone gains from having an infection, called natural immunity, varies from person to person. Some early evidence suggests natural immunity may not last very long.
- While data is limited, it appears that previously infected individuals are at risk of reinfection and therefore could benefit from vaccination. [14, 15]

Getting vaccinated can help prevent you from getting sick with COVID-19 [1]

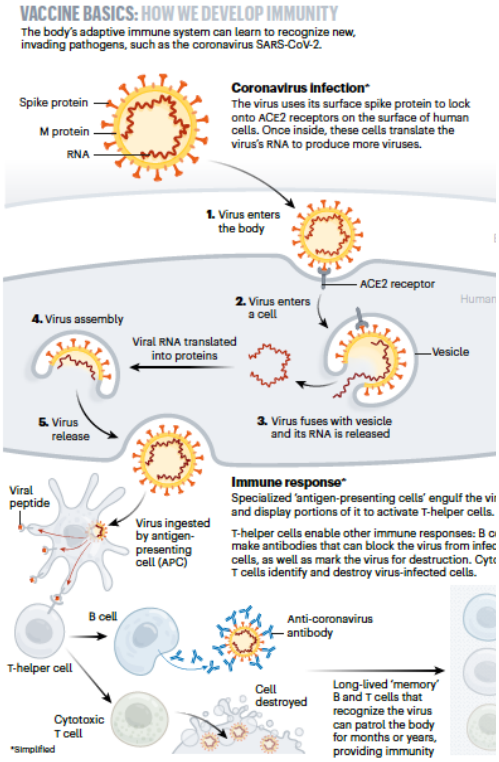
- While many people with COVID-19 have only a mild illness, others may get a severe illness or they may even die.
- There is no way to know how COVID-19 will affect you, even if you are not at increased risk of severe complications.
- If you get sick, even with an asymptomatic illness, you also may spread the disease to friends, family, and others around you while you are sick.
- COVID-19 vaccination helps protect you by creating an antibody response without having to experience sickness.

Logistical / Handling Issues

<u>The first two available vaccines will be the Pfizer and Moderna Vaccines. The following describes some of the logistical information known at this time for each of the vaccines.</u>

- **Pfizer**
  - Two doses, 21 days apart. *

<u>How Humans Develop Immunity</u>



From the website: https-//media.nature.com/original/magazine-assets/d41586-020-01221-y/d41586-020-01221-y, accessed on December 8, 2020

[2] More info about Viral Tests: *https://www.cdc.gov/coronavirus/2019-ncov/testing/diagnostic-testing.html*

[3] More info about Antibody Tests: https://www.cdc.gov/coronavirus/2019-ncov/testing/serology-overview.html

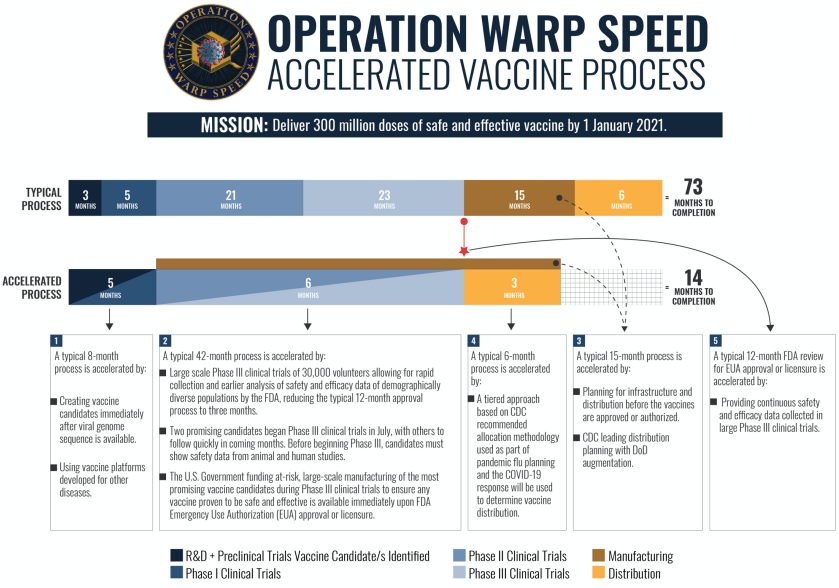
- While there are reports of benefit after receiving the first dose of Pfizer's vaccine, the study methodology was not intended to test the efficacy of only one vaccine dose. Given this, all vaccine recipients are expected to receive 2 doses of the vaccine. [14, 15]

  - Storage:
    - Ultra-cold freezer (-94º F) for up to six (6) months [4]
    - Refrigerator (35.6º-46.4º F) for up to 5 days (120 hours) [4]
    - Pfizer Shipper container for up to 15 days with dry ice refreshing
      - These are a 16"x16"x22" distribution system lined with dry ice; may hold up to 5000 doses
    - Needs to be reconstituted with 1.8 ml of normal saline, and then must be used within six (6) hours [4]
    - Once reconstituted, each vial holds 5 doses of vaccine [4]

- **Moderna**
  - Two doses, 28 days apart. *
  - Storage
    - Standard freezer (-4 º F) for up to 6 months
    - Refrigerator (35.6 º -46.4 º F) for up to 30 days
    - Can be kept at room temperature for up to 12 hours.
  - No reconstitution required.

*All trials were based on the "prime and boost" model of vaccination in which an initial dose is provided, followed by a second dose several weeks later. No efficacy information is available regarding the protection after a single dose of the vaccine and no current plans exist for these two vaccines that rely on a single dose of the vaccine. [14,15]

Process of Developing the Vaccines



US Department of Defense website: https://media.defense.gov/2020/Aug/13/2002476369/-1/-1/0/200813-D-ZZ999-100.JPG, accessed on December 8, 2020

[4] "Pfizer BioNTech Vaccine: Storage, Handling and Administration" presentation on October 20, 2020

Background: Parallel Process Vaccine Development [5]

- An innovative feature of the COVID-19 vaccine development program is that several processes have overlapped rather than occurred in a slower, step-by-step series.
- This was due, in part, to significant funding investment that enabled processes such as mandatory manufacturing plant inspections, development of distribution processes and/or vaccine production to occur prior to the formal Emergency Use Authorization (EUA) review process.
- The end result is a vaccine available for deployment almost immediately following EUA approval.
- It is important to recognize that this parallel processing HAS NOT affected or altered the scientific process of testing the vaccine. The FDA required all vaccine manufacturers to perform pre-clinical trials testing safety and efficacy in non-human primates, followed by Phase 1, Phase 2, and Phase 3 clinical trials. Each phase of the clinical trial process is intended to answer questions surrounding safety and efficacy.
    - Phase 1 trials introduce the vaccine to a small group of healthy volunteers (up to 100) to test the safety of the therapy in healthy subjects.
    - Phase 2 trials administer the vaccine to a larger group of volunteers (usually hundreds) in an effort to determine the proper dose of the vaccine by evaluating the immune response to therapy.
    - Phase 3 trials introduce the vaccine to an even larger group of volunteers (usually in the 1000s to 10,000s) and compare this group's response to the vaccine in comparison to that of a similar group who received a placebo. The major goals of Phase 3 trials are to test the efficacy of the vaccine.
        - For more information regarding basic information regarding clinical trials, please refer to this link: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics.
- All vaccine manufacturers followed this common process.
- The one element of the process that was amended is that Phase 3 trials may last up to 3 years. In other vaccine or drug trials, this duration of the Phase 3 trial is intended to determine the **duration** of effect, or the **duration** of protection.
- It is essential to recognize that the duration of Phase 3 trials IS NOT intended to learn about safety or adverse effects of the vaccine, **but rather duration of protection**. Experience with other vaccines reveals that most if not all of the adverse effects related to vaccination occur within 6 weeks of receiving the vaccine. The FDA required that vaccine manufacturers extended their Phase 3 trials to 8 weeks to ensure possible adverse reactions would be identified.
- What this change in process will admittedly do is limit our understanding of HOW LONG protection from the vaccine will last. We will not know when we receive the vaccine if we will require a second series of vaccine in the future. This information will be determined but will be tested in parallel process to the implementation of the vaccination.

[5] Morita J, Belongia "America's Last Line of Defense for a Safe Vaccine" *Scientific American* From the Website https://www.scientificamerican.com/article/americas-last-line-of-defense-for-a-safe-vaccine/, accessed on December 8, 2020

Technology of the Vaccines

Receiving an mRNA vaccine will not alter your DNA [1]

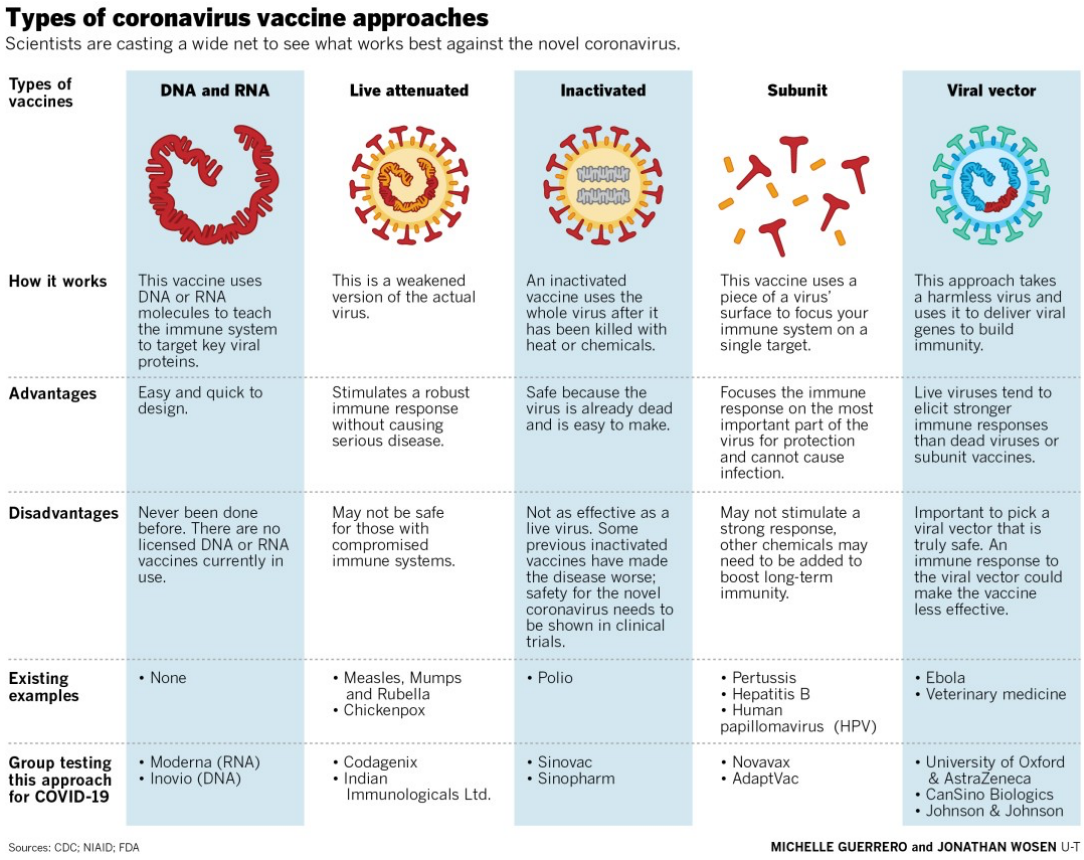
https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html

- mRNA stands for messenger ribonucleic acid and can most easily be described as instructions for how to make a protein or even just a piece of a protein.
- mRNA is not able to alter or modify a person's genetic makeup (DNA).
- The mRNA from a COVID-19 vaccine never enter the nucleus of the cell, which is where our DNA is kept.
    - This means that the mRNA does not affect or interact with our DNA in any way.
- Safety is further enhanced by the transient life of the mRNA particle which metabolically decay within a few days. [7]
- COVID-19 vaccines that use mRNA work with the body's natural defenses to safely develop protection (immunity) to disease.
- Therapeutic mRNA technologies were first considered in 1989 with mRNA vaccine platforms considered a short time later. [6]
- The first successful animal studies of mRNA vaccines were performed in 1993 with development of an influenza vaccine. [7]
- The first successful Phase 1 clinical trial of mRNA vaccine in humans was an mRNA vaccine against rabies in 2017. [7]
- Subsequent Phase 1 trials have evaluated and proven safety and efficacy in humans receiving mRNA influenza and Zika vaccines. [8]

The first released vaccines are expected to be mRNA vaccines, but additional vaccine technologies will be released in the near future. For information about the technology being used for all types of coronavirus vaccines, please refer to the following Journal of the American Medical Association (JAMA) video on YouTube at: https://www.youtube.com/watch?v=KMc3vL_MIeo&feature=youtu.be

[6] Schlake T, et al. "Developing mRNA-Vaccine Technologies", *RNA Biology*, 9:11 November 2012
[7] Albere M, et al "Safety and Immunogenicity of a mRNA Rabies Vaccine in Healthy Adults: an Open-Label, Non-Randomized, Prospective, First-in-Human Phase 1 Clinical Trial", *The Lancet*, Vol 390, September 23, 2017
[8] Pardi N, et al "mRNA Vaccines – A New Era in Vaccinology" *Nature Review,* 17:4 April 2018

Types of Coronavirus Vaccines in Production and Their Mechanism of Action



Types of coronavirus vaccine approaches

Scientists are casting a wide net to see what works best against the novel coronavirus.

Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
How it works	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not be safe for those with compromised immune systems.	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.
Existing examples	• None	• Measles, Mumps and Rubella • Chickenpox	• Polio	• Pertussis • Hepatitis B • Human papillomavirus (HPV)	• Ebola • Veterinary medicine
Group testing this approach for COVID-19	• Moderna (RNA) • Inovio (DNA)	• Codagenix • Indian Immunologicals Ltd.	• Sinovac • Sinopharm	• Novavax • AdaptVac	• University of Oxford & AstraZeneca • CanSino Biologics • Johnson & Johnson

Sources: CDC; NIAID; FDA

MICHELLE GUERRERO and JONATHAN WOSEN U-T

From the website: https-//www.sandiegouniontribune.com/news/science/story/2020-06-06/race-for-vaccine. Accessed December, 8 2020

Vaccine Safety

Post-vaccination symptoms usually occur very early after vaccination, most commonly within the first 24 hours but as late as 6 weeks later. All of the Phase 3 clinical trials lasted for at least 8 weeks in an effort to learn all of the potential adverse effects related to receiving the vaccine.

Safety information for first 2 vaccines is as follows:

- Pfizer Safety
  - Well tolerated across all populations (43,000 participants enrolled); no serious safety concerns observed.
  - Primary post-vaccination symptoms: *fatigue (4.6%), chills (2.1% in the 16-55 year old age group) and headache (3.2%).* [9,10,12,14, 15] **
  - The FDA grades the severity of vaccine reactions. Grade 3 (serious) adverse events are the most serious enough to prevent the vaccine recipient from performing their normal daily activities. The only two Grade 3 adverse reactions observed with a frequency over

[9] Dr. Dora Mills, "COVID-19 Vaccines – MaineHealth Clinical Update 12/1/2020" presented December 2, 2020

[10] From the website, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine, accessed on December 8, 2020

2% were fatigue (at 3.8%) and headache (at a frequency of 2.0%). Older adults had fewer adverse events. [9,10, 12,14, 15]
    - The onset of systemic reactions occurred within 1-2 days from vaccination with a median duration of 1 day. [15]
  - The Pfizer vaccine was first released in the UK and during early implementation, two individuals with history of anaphylaxis suffered allergy/anaphylactoid symptoms shortly after receiving the vaccine. These reactions were treated on site. Based on this experience, the FDA has asked all individuals to advise their vaccine provider if they have any allergies prior to receiving the vaccine. In addition, the FDA has added that the anyone in the following to groups should NOT receive the vaccine:
    - Anyone who has had a severe allergic reaction after receiving a previous dose of this vaccine, and
    - Anyone who has had a severe allergic reaction to any ingredient of this vaccine
      - The list of Pfizer vaccine ingredients is as follows: mRNA, lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3- phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose [11]
  - Grade 4 reactions are reactions that require emergent care or hospitalization. No one who received this vaccine suffered a Grade 4 reaction during Phase 1 trials. [12,14, 15]
    - During Phase 3 trials, 2 patients in the vaccine group and 2 patients in the placebo groups both suffered grade 4 fevers. [15]

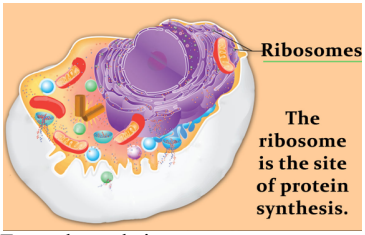
- Moderna Safety
  - Review of solicited adverse events indicated that the vaccine was generally well tolerated (30,351 participants enrolled); no serious safety concerns observed.
  - Primary post-vaccination symptoms: *injection site pain, fever, fatigue, chills, myalgia, arthralgia (joint pain), headache.*[9,12,13] **
    - All adverse reactions are more common in the 65 and younger age group. [16]
  - Grade 3 (serious) events occurring at a frequency greater than or equal to 2% after the first dose included injection site pain (2.7%). After the second dose, these included fatigue (9.7%), myalgia (muscle pain) (9.0%), arthralgia (5.2%), headache (4.5%), pain (4.1%) and erythema/redness at the injection site. [16]
    - Local reactions were most likely 1-2 days after vaccination and generally persisted for a median of 1-3 days. Systemic reactions were most likely to occur within 1-2 days of receiving the vaccine and persisted for a median of 1-2 days. [16]
  - No one who received this vaccine suffered a Grade 4 reaction during Phase 1 trials. [12]
    - During phase 3 trials, there was a 0.1% incidence of grade 4 fevers in BOTH the placebo and vaccine group as well as 1 vaccine patient who suffered grade 4 fatigue, 1 vaccine patient who suffered grade 4 arthralgias (joint pains) and 1 vaccine patient who suffered grade 4 nausea and vomiting.[16]

[11] "Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 16 years of Age and Older" from the website: https://www.fda.gov/media/144414/download
[12] Walsh E, et. al, "Safety and Immunogenicity of Two RNA-Based COVID-19 Vaccine Candidates" *NEJM,* October 14, 2020
[13] From the website, https://investors.modernatx.com/node/10316/pdf, accessed December 8, 2020

**** Due to the possibility of viral syndrome-type post-vaccination symptoms, consider staggering vaccination implementation for public safety personnel in order to ensure adequate duty ranks**.

Please also refer to the section above regarding the technology and safety of mRNA vaccines. mRNA vaccines were initially developed in the 1990s. The mRNA used in these vaccines is wrapped in a lipid nanoparticle that maintains the mRNA stability. The wrapped mRNA enters a cell and is then picked up by cellular ribosomes. Ribosomes are outside of the cell's nucleus and therefore distant from the cell's DNA. This technology provides our ribosomes with mRNA instructions for making the SARS-CoV-2 (coronavirus) spike protein. When our cells receive these instructions, they briefly produce the spike protein. Our immune system recognizes the spike protein as "foreign" and makes antibodies to destroy it. If we get infected with the real virus, our immune system recognizes the threat and is already prepared to fight it. mRNA is very short-lived, does not enter the cell nucleus and has no direct interaction with a patient's DNA. In fact, cold storage is required to keep the mRNA stable enough to be effective before it rapidly degrades. This vaccine technology WILL NOT alter your DNA or genetic code. There are a number of mRNA vaccines currently being studied, including a Zika vaccine, a CMV vaccine and some of the influenza and rabies vaccines. Experience from these vaccines proves both the safety and efficacy of this technology.

For more information on the mRNA technology, please refer to the CDC's website at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html.



From the website: https://biologywise.com/ribosomes-function, accessed December 8, 2020

From the website, http://www.nomeofficinapolitica.it/wpcontent/uploads/2020/10/Vaccini_NYT.pdf, accessed December 8, 2020

Vaccine Efficacy

This section focuses on the first two released vaccines, the mRNA vaccines from Pfizer and Moderna. As new vaccines are released, this section will be updated.

-Pfizer Efficacy:

- 95% effective
  - 170 cases of COID-19 out of 43,000 participants
    - 162 in the placebo group
    - 8 in the vaccine group
  - 10 severe cases of COVID-19 [14, 15]
    - 9 in the placebo group – 7 total hospitalized
    - 1 in the vaccine group – not hospitalized [14,15]
- Consistent across age, gender, demographics; 94% efficacy in adults over 65. [9,10,15,14]

Pfizer Definition of Severe Case Include any of the Following: [15]

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

[14] Polack et al., "Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine" *NEJM*, December 10, 2020 https://www.nejm.org/doi/full/10.1056/NEJMoa2034577

[15]"Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020 FDA Briefing Document Pfizer-BioNTech COVID-19 Vaccine Sponsor" from the website: https://www.fda.gov/media/144245/download, accessed 12-9-2020

-Moderna Efficacy:

- 94.1% effective[16]
  - 196 cases of COVID-19 out of 30,351 participants
    - 185 in the placebo group
    - 11 in the vaccine group
  - Of the 30 severe cases, all occurred in the placebo group.[16]
    - 1 death occurred due to COVID-19 in the placebo group.
- The 95 COVID-19 cases included 15 older adults (ages 65+) and 20 participants identifying as being from diverse communities. [9,12]

Moderna Definition of Severe COVID-19 Case [16]

Patient meets definition of COVID-19 PLUS any one of the following conditions:

- Clinical signs of severe systemic illness, respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg; OR
- Respiratory failure of Acute Respiratory Distress Syndrome (ARDS) [defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)]; evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors); OR
- Significant acute renal, hepatic, or neurologic dysfunction; OR •
- Admission to intensive care unit or death.

Maine EMS and the MDPB hope that this clinical bulletin has been informative and supportive of your decision-making process. The advent of a vaccination campaign allows us to collectively transition from a defensive posture against this pandemic to an offensive posture and thus move back toward our normal lives. *This does not mean we will immediately reduce our protective postures* including screening for PUIs, universal masking of patients and EMS clinicians, airborne precautions when caring for PUIs/known positives, performing aerosol-generating procedures, and encountering those unable to comply with masks, hand washing, distancing, etc. Herd immunity, or resistance to the spread of an infectious disease due to pre-existing immunity of a high proportion of individuals, is achieved only after an estimated 75% of the population is vaccinated. Once this goal is achieved, we will be able to return to some form of our normal activities. Thank you for reviewing this information, for all you have done for our state and your communities and helping us collectively achieve the goal of herd immunity.

[16] "MRNA-1273 Sponsor Briefing Document, Vaccines and Related Biological Products Advisory Committee, Meeting Date: December 17, 2020", From the website: https://www.fda.gov/media/144452/download, Accessed on December 15, 2020