THE IMMUNIZATION PARTNERSHIP

From the Lab to Your Doctor's Office: Vaccine Development & Safety Measures Training Module Transcript

Slide 1:

Hello and welcome to Vaccine Development & Safety Measures, an educational video presented by The Immunization Partnership.

Slide 2:

The Immunization Partnership is a Texas-based non-profit dedicated to helping individuals, physicians, and others with an interest in immunizations protect their communities from vaccine-preventable diseases.

All across Texas, The Immunization Partnership conducts educational community forums and researches immunization best practices.

Slide 3:

This presentation is made possible through partnerships and funding from our listed supporters.

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Slide 6:

Before we get started, here is the disclaimer letting viewers know all speakers and individuals on the planning committee have no disclosed conflicts of interest. Additionally, this presentation is for educational use only and does not constitute legal or medical advice.

Slide 7:

This presentation will cover the following topics:

1.Vaccine Development

2.Vaccine Safety Monitoring

3.The Vaccine Adverse Event Reporting System (VAERS)

4.The Vaccine Injury Compensation Program

5.Development of the COVID-19 Vaccines

6.Helpful Resources

Slide 8:

Many people have questions about the safety of vaccines. When we are discussing vaccine safety, it is important to understand what exactly we mean when we use the word "safe".

A common definition of the word "safe" is harmless[1]. Vaccines commonly cause uncomfortable side effects – though these side effects, like tenderness at the injection site, are very mild and temporary. However, vaccines may also cause more severe side effects, though these events are incredibly rare. Therefore, using the definition of "harmless" to describe a vaccine isn't accurate, as no vaccine is one hundred percent safe. A better definition of safe when referring to vaccines, or most medical interventions, is "having been preserved from a real danger"[1]. This is another way of saying that the benefits of a vaccine must outweigh any risks. It is important to keep this in mind when discussing vaccines. Almost all vaccine-preventable illnesses have the risk of severe complications, including death. Therefore, a vaccine that will prevent that illness and its potential complications provides a greater benefit than risk.

Still, people may have concerns about vaccine safety. Many concerns and questions are related to how vaccines are made. On whom and for how long is a vaccine tested before it becomes available to the general public? Who tracks any side effects and makes sure vaccines continue to be safe after they are approved? How do we know if there will be any long-term impacts from vaccines?

Addressing these common questions is essential to explaining the ways in which we know that vaccines are safe.

Slide 9:

To better understand the ways in which vaccines are safe, we'll start by learning about the stages of vaccine development.

Slide 10:

Here you will see a simplified overview of the stages of vaccine development, starting with the initial Exploratory Stage and ending with Review and Licensure.

Every vaccine starts out in the Exploratory Stage and then moves into the Pre-Clinical Stage. Both the Exploratory and Pre-Clinical stages are focused on laboratory work and do not involve humans. After the Pre-Clinical Stage, vaccines enter Clinical Trials, where the vaccine candidate is studied in human

participants. Each vaccine will go through Phase 1, 2, and 3 of clinical trials, with each phase growing in participant size. Finally, data from the clinical trials is reviewed as part of the Review & Licensure stages.

Every vaccine must go through each of these stages before it can be given approval by the FDA in the United States. Each stage is critical to the development of both safe and effective vaccines.

Slide 11:

The first step for any vaccine is the Exploratory Stage, which may also be referred to as the "Research" or Discovery Stage[2]. The exploratory stage involves basic laboratory research, often conducted at a research university, medical setting, or small biotech company by federally funded academic or government researchers. During the Exploratory Stage, scientists work to create the beginnings of a vaccine by developing a method for the vaccine to prevent whatever disease they are working on.[2]

In order to develop a vaccine, scientists must understand how the disease affects the human body. Part of this work involves identifying an antigen from the virus or bacteria that can be used to develop a successful vaccine. Antigens are proteins that are found on the surface of a pathogen (either a virus or bacteria) that illicit the immune response when they "invade" the human body.[3] By identifying the antigen, researchers can begin to explore ways to use that antigen in the development of a vaccine. Antigens used in a vaccine may include virus-like particles, weakened viruses or bacteria, or other substances taken from the original bacteria or virus.[4]

Scientists may spend years testing their ideas to see if they will work and may have to adjust as they measure success. Many vaccines never make it beyond the Exploratory Stage. However, if the exploratory science that is performed reveals a practical solution in preventing a disease, a vaccine candidate may move forward into the Pre-Clinical stage.[5]

Photo from: https://phil.cdc.gov/Details.aspx?pid=23210

Slide 12:

Once a vaccine candidate has shown promise in the Exploratory Stage, it moves into the Pre-Clinical stage, where it undergoes rigorous testing for both basic safety and efficacy.[4] During the Pre-Clinical stage, researchers perform additional laboratory tests using tissue and cell cultures, and finally move into testing the vaccine in animals, often mice and monkeys.[5] These tests help identify any concerns related to vaccine safety as well as help determine how effective the vaccine is at preventing disease. Testing the vaccine in animals helps researchers to understand how effective it is and may lead to adjustments of dosing.[2] Testing vaccine effectiveness during this stage may involve the animals being directly infected with the pathogen (virus or bacteria) to better understand how well the vaccine functions when it comes to preventing the disease.[4]

During the pre-clinical phase, the work of scientists is continually reported, shared, and reviewed by other scientists through peer-reviewed journal articles and presentations. At this time, scientists in the private sector working for pharmaceutical companies may approach researchers if they believe the vaccine candidate to be worthy and may partner to expand the research and work.[5] This leads into the IND Application, which is a requirement before moving into the Clinical Trials. A sponsor, generally a private pharmaceutical company, will submit an application for an Investigational New Drug or IND to the Food and Drug Administration (FDA).[4] This application includes details on the manufacturing and

testing processes for the vaccine, summarizes the results of previous laboratory studies, and lays out the plan for the proposed vaccine study in the clinical trials. Finally, an institutional review board (IRB) must approve the clinical protocol for the proposed clinical studies. The FDA has 30 days to approve the IND application.[4] Once approved, the vaccine enters human clinical trials.

image from: https://www.smartmarketnews.com/news/2020-02-13/uk-scientists-uk-team-tests-coronavirus-vaccine-on-mice

Slide 13:

Before we move into the phases of clinical trials, it's important to review how they are configured. Researchers use what is called "Placebo-controlled" trials when studying vaccines in human participants. In a placebo-controlled study, some participants receive the vaccine being tested – this is known as the "experimental group". Other participants receive a placebo, often a vaccine that is already approved, a saline-solution, or a portion of the vaccine being studied without its "active" ingredients that illicit an immune response. Individuals receiving the placebo are known as the "control group".[5]

It's important that researchers have a control group so they can have a comparison to determine what the true effects of the vaccine really are. The experimental group and the control group are made up of similar participants – meaning both groups have similar numbers of individuals of certain ages, race and ethnicity, health status or conditions, and sex. This is done to ensure that when researchers compare any differences between the two groups, they can attribute differences to the vaccine, and not to vast differences in the study participants themselves. This also helps ensure that the vaccine is safe and effective for a wide variety of people. Researchers will compare the differences between the control and experimental groups in terms of side effects, infection, and any development of disease which may result in sickness, hospitalization, or death.[5]

Finally, placebo-controlled trials are randomized and double-blinded. This means that participants are placed into either the experimental or control group at random (through a data-driven process) and neither the study participants or researchers know who belongs to each group until the trial is complete. This is done to ensure that bias does not affect the results of the trials. For example, if an individual knows that they are in the experimental group and did receive the vaccine, they may be more likely to report side effects such as a headache, than if they did not know which group they belonged to. This headache may be from the vaccine, or it may be coincidental. By keeping the groups hidden, researchers can compare side effect reports and rates between both the experimental and placebo groups and determine if there is a significant difference caused by the vaccine.[5]

In order to keep participant groups blinded throughout the study, while also tracking the outcomes of each individual, study participants are often assigned a code for tracking purposes as are the vials of the vaccine and placebo administered in the study. This is also done to ensure that there is no physical difference in the vials containing the vaccine or placebo. Individuals creating and managing the codes and vials are different from those administering the vaccines and placebo. Aside from the successful completion of the study, it is only in the event of serious side effects that the trial is paused, and the code is broken to reveal who received either the vaccine or placebo.[5]

Slide 14:

Testing the vaccine in humans begins with Phase 1 of Clinical Trails. During Phase 1, the vaccine is administered to a small number of healthy adults to answer two main questions. First, and most importantly, is the vaccine safe? Second, is the vaccine effective – meaning, does it generate the expected immune response?[2,5]

Phase 1 clinical trials include the use of placebos and may be non-blinded, meaning that either researchers or participants know whether they have received either a placebo or the vaccine. Additionally, researchers may use the "challenge model" which involves infecting participants with the pathogen after receiving the vaccine.[4] This is not always ethically possible and is not a component of all vaccine clinical trials. For example, if the disease hoping to be prevented by the vaccine does not have an available treatment or isn't curable, researchers would not seek to actively infect participants as part of the study.

During Phase 1, researchers carefully monitor participants and control the study conditions. The immune response generated by the vaccine is studied so researchers can understand if differences in dosing are needed to improve how well the vaccine works in people. Additionally, any initial side effects observed in participants may alert researchers that modifications are needed to the vaccine.[5]

Another important part of vaccine development that occurs during Phase 1 Clinical Trials involves the pharmaceutical company studying the best ways to produce large enough amounts of the vaccine for later trial phases. Additionally, they must study and determine if the vaccine will need any preservatives or stabilizers so that it does not break down, as well as any adjuvants that may be necessary to help create a strong immune response. This step is very important because any preservatives, stabilizers, or adjuvants that will be used in the final vaccine must also be included and studied as part of the trials.[5]

Phase 1 clinical trials generally take one to two years to complete.

Image from: https://www.latimes.com/science/story/2020-07-14/clinical-trial-results-indicate-moderna-vaccine-is-on-the-right-track

Slide 15:

When a vaccine candidate moves into Phase 2 of Clinical Trials, more participants, generally several hundred, are included in the study. A more diverse set of participants is recruited as the vaccine candidate moves into Phase 2, so researchers can study how the vaccine affects individual with different health statuses, different demographic backgrounds, and people who are likely to be at risk for acquiring the disease in their day-to-day life.[2]

Participants in Phase 2 are included in randomized-controlled studies, where some participants will receive the vaccine and others will receive the placebo (referred to as the "control group").[4] Additionally, as researchers are working to identify the best dosage for a vaccine, participants may also receive different dosing for the vaccine. With this study set-up, researchers are then able to compare the data from individuals who did and didn't receive the vaccine, as well as any differences observed between dosing.[5]

During Phase 2, researchers continue to monitor safety and make note of any short-term side effects. How well the vaccine produces an immune response is a critical aspect of this trial stage, and researchers use standardized testing to validate the results comparing dosing between study

participants. This helps researchers understand the relationship between the dose administered and the immune response generated by that dose amount.[5]

Manufacturing plans for the vaccine may occur concurrently with the human trials and at this stage, scientists and the pharmaceutical company continue to plan the methods for manufacturing the vaccine, stabilization of the product, and packaging and vials. During this stage, it is important to establish manufacturing consistency, so each lot of produced vaccines is the same.[5]

Slide 16:

Phase 3 is the final phase of development before a vaccine candidate can be reviewed and approved for licensure. Phase 3 studies include hundreds of thousands of people and are composed of study participants that are statistically similar to the population that will receive the vaccine.[2,5]

The size of the study during Phase 3 is calculated using factors of the frequency the disease occurs in the population, estimated dropout rates of study participants, and the ability of the different versions of the vaccine candidate to show differences. The final number of participants calculated for the study ensures that statistical differences between the experimental group receiving the vaccine, and the control group can be observed for comparison purposes.[5] Therefore, the study size of Phase 3 trials is different and unique to each vaccine candidate.

As with previous study phases, both vaccine safety and efficacy are monitored during Phase 3 trials. While researchers may have some understanding of common side effects from the vaccine after Phases 1 and 2, Phase 3 trials can help identify any rare side effects that may only appear among thousands and thousands of study participants. Additionally, greater sample size data helps researchers more fully understand how common and severe side effects of the vaccine will be.[4]

The double-blinded controlled study also allows researchers to compare the immune response outcomes of those who received the vaccine and those who received the placebo. Metrics like the number of confirmed cases of the illness in the vaccinated versus unvaccinated groups help researchers gauge how well the vaccine works at preventing illness.[5] Other factors such as hospitalizations or death (from the illness) can help researchers understand how well the vaccine protects against serious illness. This is the final stage of testing before vaccine data is reviewed for approval and generally takes three to four years to complete.

Slide 17:

After the successful completion of Phase 3 clinical trials, the company developing the vaccine will spend months to years reviewing and analyzing their own data before submitting a Biologics License Application (BLA) to the U.S. Food & Drug Administration (FDA) for review. The BLA is the first step in a company seeking approval to distribute their vaccine in the United States.[2]

The FDA receives the data submitted to determine if the vaccine has been proven to be both safe and effective for the populations that it is intended to reach. Manufacturing processes are also an important factor in the BLA and review, as the FDA must ensure that the manufacturing processes and facility status will ensure product quality and consistency.[2]

At the heart of the FDA's consideration of approving a vaccine is whether the benefits of the vaccine outweigh any risks. Part of this risk analysis often involves how serious the disease is that is prevented

by the vaccine. The scientific team of the FDA that is responsible for reviewing Biologics License Applications includes physicians, chemists, statisticians, pharmacologists/toxicologists, microbiologists, experts in post marketing safety, clinical study site inspectors, manufacturing and facility inspectors, and labeling and communications experts.[2]

Once the FDA gives approval to a company's BLA, the company is permitted to distribute and market the vaccine for the population in which it was approved. This is the typical route for approval of any vaccine in the United States. In instances of public health emergencies, some vaccines may be granted "Emergency Use Authorization" or EUA status, which is not quite the same as full approval.[2] This was the case of the COVID-19 vaccines, and we will talk further about the processes of an EUA in the next section.

Slide 18:

Now that we've reviewed the details of how vaccines are developed, let's explore the ways in which vaccines are continually monitored for safety after they are approved.

Slide 19:

Vaccine safety monitoring doesn't stop once a vaccine is approved and licensed for use. While safety data from clinical trails is crucial, it's even more important for vaccine developers and the government to actively monitor vaccine safety once a vaccine begins to be administered to the public. This is done through several different mechanisms.

First, pharmaceutical companies may continue clinical trials after the vaccine has been licensed for use. This is referred to as Phase IV clinical trials.[4]

Second, the Centers for Disease Control and Prevention utilizes data from large health departments across the country to monitor any issues related to the vaccine. This is done through two different methods. One, the CDC, via local health departments in areas whose population has a high incidence of the disease, and therefore high vaccine distribution, will monitor all vaccine recipients and report back.[5] The CDC will also monitor disease data reported by every health department in the country. If an abnormal increase of disease is noticed after the vaccine is introduced, they will investigate to ensure it has not been caused by the vaccine.[5]

Slide 20:

Vaccine safety is also monitored through two major government systems.

The Vaccine Safety Datalink (VSD) is a partnership between the CDC and 8 large Healthcare Organizations, primarily on the West Coast. The VSD has a patient population of roughly 6 million and is one of the best tools to measure vaccine safety after licensure.[6] The VSD can compare data from individuals who have received the vaccine, with those who have not to detect any vaccine-related adverse events in almost real time.[6] This is done through weekly updates of VSD data to compute rates of adverse events among both vaccinated and unvaccinated individuals. If the rate of an adverse event in the vaccinated group is higher than the comparison group (those who had not received the vaccine), then the vaccine may be associated with adverse events and will be investigated further.

Finally, the Vaccine Adverse Event Reporting System (VAERS) is another method of monitoring vaccine safety in the United States. VAERS is maintained by the CDC and FDA and allows anyone to submit a report related to vaccine side effects.[5] While there are some limitations to the system, it has proven effective at being the first hint of safety concerns with past vaccines.

Slide 21:

As we just learned, VAERS is not the only method for monitoring vaccine safety in the United States. It is however, one of the tools available to everyone and therefore has its own set of positives and limitations that are important to learn about.

Slide 22:

VAERS, or the Vaccine Adverse Event Reporting System, was established by the CDC in 1990. According to the CDC, the goal of VAERS is to "detect possible signals of adverse events associated with vaccines."[7] VAERS is what's known as passive surveillance system, meaning it relies on voluntary reports to be submitted in order to be alerted of a possible problem.[7] This contrasts with active surveillance systems that seek out, or regularly check-in with health departments or healthcare providers to request status updates.

One of the unique aspects of VAERS is that it allows anyone to make a report regarding an adverse event following vaccination. This may include healthcare workers like doctors or nurses, patients who received the vaccine, or their family on behalf of the patient. The CDC monitors VAERS reports daily and will investigate any serious reports, such as those describing an event that resulted in permanent disability, hospitalization, life-threatening illness, or death. VAERS staff will follow-up to obtain medical records for these types of serious reports.[7]

The CDC uses VAERS data to do the following:[7]

•Detect new, unusual, or rare vaccine adverse events

•Monitor any increases in known adverse events

•Identify potential patient risk factors for particular types of adverse events

•Identify vaccine lots with increased numbers or types of reported adverse events

•Assess the safety of newly licensed vaccines

While the data submitted to VAERS is a valuable tool for monitoring vaccine safety, it does have its limitations as the CDC doesn't investigate causality of any VAERS report. We will talk further about the strengths and limitations of VAERS as a vaccine safety monitoring system.

Slide 23:

When weighing the pros and cons of VAERS, it is imperative to state one of the biggest limitations of the system. VAERS is unable to determine causality.[7] What does this mean? While VAERS accepts reports of adverse events following vaccination, the system is not set up to prove that the vaccine was the sole cause of the adverse event. While some adverse events may be caused by a vaccine, others may simply

be coincidence that overlapped with the time frame in which a person received a vaccine. In a vaccine clinical trial, this would be investigated to determine a true cause, but VAERS is not configured in that way.

Instead, VAERS accepts reports of adverse events without judgement of the cause or level of seriousness of the event. While VAERS is not a good tool for determining causality, it can be a useful tool in detecting unusual patterns of reporting that may indicate a need for further investigation.[7]

Slide 24:

Let's review the specific strengths and weaknesses of VAERS:

When it comes to the strengths of VAERS as a tool for monitoring vaccine safety, there are multiple factors that make it a useful tool. First, VAERS collects data from across the United States and its territories. Second, as previously stated, VAERS allows anyone to submit a report. This is a unique feature of VAERS and allows both medical staff and laypeople the same opportunity to submit a report of an adverse event following vaccination. This is different from other major reporting systems like the Vaccine Safety Datalink (VSD), which is limited to healthcare professionals. The data collected in a VAERS report is potentially useful in that it includes details about the specific vaccine administered, the person who received the vaccine, and the adverse event that was experienced. Finally, data from VAERS is made publicly available via online databases accessed on the VAERS or CDC websites.[7]

However, there are some limitations and weaknesses when discussing VAERS as a method for monitoring vaccine safety. The biggest limitation to VAERS is once again the inability to determine causality from a report of an adverse event. Without a mechanism to investigate and determine if the vaccine was the true cause of the adverse event, rates also cannot be computed for adverse events.[7] This is also due to the fact that the system is a passive surveillance system and does not consider the number of doses of the vaccine given, which again prevents the computation of rates. Additionally, while a strength of VAERS is that anyone can submit a report, that also can create issues in the quality of data reported. Some reports may lack full details or even contain inaccurate information. Reports made to VAERS are also more likely to be serious adverse events, rather than more mild and potentially more common events like migraines and skin irritation. Finally, media reports or other forms of awareness like viral social media posts may prompt a flurry of reports to VAERS, when they otherwise may have gone unreported.

Slide 25:

Some of the unique strengths of VAERS, the ability for anyone to submit a report and open access of reports to the general public, have also created opportunities for anti-vaccine organizations to spread misinformation. Since VAERS was established in 1990, anti-vaccine organizations have pointed to its existence and data as evidence that vaccines are associated with significant vaccine-related adverse events. Organizations like the National Vaccine Information Center present reports and statistics from VAERS as fact, without providing any disclaimers that the data in the system has not been verified.[8] To give a specific example of the limitations of VAERS and the dangers in giving credit to any report listed in the system, we'll provide the following scenario. If they wanted to, an individual could make a report to VAERS noting death or serious injury, from a car accident. While this car accident obviously has nothing to do with the vaccine, it can still be reported and listed in VAERS. Should a media outlet or other entity

simply report on death numbers listed in VAERS, this report would be included, when there is no association between a car accident and receiving the vaccine.

Still, even with the limitations and weaknesses of the system, VAERS remains a strong tool and often the first detection of possible problems that researchers need to investigate further with other systems like the Vaccine Safety Datalink. One of the major success stories of VAERS as a method of vaccine safety monitoring comes from the first rotavirus vaccine that was introduced in 1998. Rotashield was officially taken off the market in 1999 after causality was proven regarding some infants under the age of 12 months receiving the vaccine and very quickly developing an intestinal blockage condition known as intussusception.[9] It was reports from VAERS that helped confirm the issue needed further investigation as parents and healthcare professionals were encouraged to report any gastrointestinal complaint to VAERS after receiving Rotashield. Rotashield is no longer available for use in the United States.[8]

Slide 26:

While VAERS remains a powerful tool and often is a source of initial detection of a vaccine safety concern, the system's data has also been exploited to spread disinformation and contribute to vaccine hesitancy.

On this slide you will see images taken from two different online platforms, both of which cite numbers from VAERS. You may also notice that these platforms fail to mention that reports from VAERS are unverified. Anti-vax groups have leaned heavily on VAERS with the COVID-19 vaccine specifically, and are encouraging individuals to submit reports, whether real or not.[8]

After reviewing VAERS and its limitations, you can understand why presenting data from VAERS without a disclaimer is inappropriate, and only works to undermine the public's trust in vaccines. This is important to keep in mind the next time you view material making claims about the number of vaccine-related adverse events – always check the source and HOW the authors are presenting the data. And remember, VAERS cannot prove causality.

Slide 27:

Now that we've reviewed vaccine safety monitoring, let's discuss the National Vaccine Injury Compensation Program.

Slide 28:

The Vaccine Injury Compensation Program was created in the late 1980s, as part of the National Childhood Vaccine Injury Act of 1986 that Congress passed.[10] Reviewing what took place in the decades prior to the Vaccine Injury Compensation Program being created is crucial to understanding why the program was established and what problems it was meant to address.

In short, the Vaccine Injury Compensation Program was created after lawsuits against vaccine manufacturers threatened to cause shortages of the United States' vaccine supply as some vaccine manufacturers began to withdraw from vaccine production.[10] The longer explanation involves a rise in claims of vaccine-related illnesses and injuries in the decades following the United States' successful initial vaccine campaigns in the late 1950s and early 1960s. Experts of the era explain that as public memory of the severity of vaccine-preventable diseases faded, the risk-analysis of vaccines changed and more vaccine-injury lawsuits began to pop up.[11] As we've covered in our section on safety monitoring,

particularly passive systems, it is often difficult, if not impossible to determine true causality for many vaccine-injury claims. This resulted in more lawsuits against vaccine manufacturers, with the average claim rising from $10 million in the 1970s to $47 million in the mid 1980s.[11] Since a causal link is often difficult to prove in these cases, damages were sometimes awarded “despite the absence of scientific evidence”[11] As drug and vaccine manufacturers looked to the future, the time-consuming and costly process of vaccine development began to look increasingly risky, and manufactures started to withdraw from vaccine development and production.

This resulted in public health concern about the country’s vaccine supply and resulted in Congress acting through legislation in the late 1980s. We’ll discuss the details of the program on the next slide, but in summary, this legislation changed the entity who would receive a claim of vaccine injury or illness from individual vaccine manufactures, to the government, via The Vaccine Injury Compensation Program.

Slide 29:

While the Vaccine Injury Compensation Program was created to address the legal threat to vaccine manufacturers that began to hamper the United States' vaccine supply, it was also created to simplify the legal process for individuals making claims. In fact, Congress charged the program with addressing vaccine-claims, "quickly, easily, and with certainty and generosity".[11]

Any individual who has received a covered vaccine and believes they were injured as a result of the vaccine may file a petition. Additionally, parents/guardians may file on behalf of their children, disabled adults, and those who are deceased.[10]

Three government entities are involved in the Vaccine Injury Compensation Program.

The Department of Health and Human Services (HHS) oversees and administers the program.

The Department of Justice (DOJ) represents HHS in Court and the US Court of Federal Claims (the Court) makes the final decision regarding whether a petition should be compensated or not.

In order to make a claim, the vaccine must be covered, and the petition must be filed within 3 years after the first symptom of the alleged vaccine injury. The petition may also be filed within 2 years of death and 4 years after the first symptom of the alleged vaccine injury that resulted in death.[10]

The Vaccine Injury Compensation Program covers most vaccines that are routinely administered in the United States. For a vaccine to be covered under the program, the CDC must recommend the category of vaccine for routine administration to children or pregnant women.[10] A full list of covered vaccines is available on the Health Resources & Services Administration website.

Slide 30:

Now that we’ve reviewed the reasons that the Vaccine Injury Compensation Program was created, let’s review the process of a claim in detail.

The process is initiated when an individual files a claim with the U.S. Court of Federal Claims.[10,12]

From there, medical staff with the Department of Health and Human Services review the petition to determine if it meets the medical criteria for compensation and make a preliminary recommendation.[10,12]

Next, the Department of Justice develops a report that includes both the medical recommendation from HHS and a legal analysis of the claim. This report is then submitted to the U.S. Court of Federal Claims, otherwise referred to simply as the Court. [10,12]

The report is then presented to a court-appointed special master who must decide whether the petitioner should be compensated. A hearing is held in which both parties may present evidence. If the Court decides to award compensation, the special master will determine the amount and type of compensation. [10,12]

Finally, if compensation has been awarded, the Court will order the Department of Health and Human Services to award compensation. If a petitioner's claim is denied and they want to take the petitioner further, they may appeal the decision and file a new claim in civil court against the vaccine manufacturer or healthcare provider who administered the vaccine. [10,12]

Slide 31:

Finally, let's review compensation number trends for the Program and discuss what they really mean.

Until recently, the Vaccine Injury Compensation Program did not compensate a majority of claims submitted to it. A 2015 analysis from Nora Engstrom of Stanford Law School found that roughly a quarter of petitions filed with the program were awarded compensation.[11] However, there has been a recent shift in the portion of claims receiving compensation. From 2015 – 2019, the Vaccine Injury Compensation Program compensated 77% of claims made.[11] Supporters of the program argue that this means the program is working as intended – to simplify the claims process. However these numbers are also often cited by anti-vax organizations as additional evidence that vaccines are not safe.

In order to understand why that argument isn't sound, let's review some more details of making a claim to the program, and how the legal requirements for compensation are different than a traditional civil or criminal court setting. The Vaccine Injury Table is a tool created as part of the program that helps standardize the compensation process, while also reducing the time it takes to receive compensation.[11] The table lists illnesses, disabilities, and injuries that are presumed to be caused by each specific vaccine, if no other cause is found. According to the program, if the first symptom of the injuries/conditions occurred within the specified time periods and the injury meets the definition provided in the table, the Program may presume that the vaccine caused the injury or condition unless other cause is found. If the injury/condition of the claim is not listed in the Vaccine Injury Table or does not meet the table requirements, the claim must prove evidence through other means, such as expert witness testimony, medical records, or a medical opinion.[10]

If the petitioner's claim meets the criteria of the Table and no other cause is found, they receive what is known as presumption of causation, which is a unique legal factor of the Program.[10] Compared to a criminal case where the defendant (in this case the vaccine cited in the petition) is presumed innocent until proven otherwise, the VICP presumes that the vaccination was the cause unless proven otherwise. This is why the Vaccine Injury Compensation Program points out that receiving compensation does not necessarily mean that the vaccine caused the alleged harm.[11]

Slide 32:

Now we'll discuss the development of the three COVID-19 vaccines authorized for emergency use as of July 19th 2021.

Slide 33:

As of July 19th, 2021, there are 3 different COVID-19 vaccines currently available in the United States. Because of the pandemic, all three of the COVID-19 vaccines have been granted Emergency Use Authorization or (EUA) by the Food & Drug Administration (FDA). As part of the FDA's evaluation of COVID-19 vaccine EUA requests, they analyzed the controls, chemistry, and manufacturing for each vaccine. To ensure proper and current compliance in the vaccine manufacturing process, the FDA conducted site visits, reviewed records, and previous compliance history.13

In guidance released by the FDA in October 2020, entitled Emergency Use Authorization for Vaccines to Prevent COVID-19, it was made clear that an EUA authorization for the COVID-19 vaccine had to demonstrate two important aspects:

1.There must have been "adequate manufacturing information to ensure it's quality and consistency."[13]

2.The FDA determined that "the vaccine's benefits outweigh its risks based on at least one well-designed Phase 3 clinical trial," demonstrating it's vaccine safety and efficacy in a "clear and compelling manner."[13]

In this slide you'll notice that Pfizer/ Biontech and Moderna received EUA authorization within a week of one another in December, 2020, while the Johnson & Johnson vaccine was authorized in the beginning of 2021.

•Pfizer/Bio-n-Tech, EUA authorization: Dec. 11, 2020, 2 dose regimen

•Moderna, EUA authorization: Dec. 18, 2020, 2 dose regimen

•J&J, EUA authorized: Feb. 11, 2021, only 1 dose needed

Next, we'll discuss the EUA authorization process in more detail.

Slide 34:

The EUA authorization process, carried out by the FDA Commissioner, consists of 5 main steps:

1.Determination of Emergency: One of the four situations must be in place[14,16] –

- The Department of Defense (DoD) Secretary issues a determination of military emergency or significant potential for military emergency
- The Department of Homeland Security (DHS) Secretary issues a determination of domestic emergency or significant potential for domestic emergency.
- The Department of Health and Human Services (HHS) Secretary issues a determination of public health emergency or significant potential for public health emergency
- The Department of Homeland Security (DHS) Secretary issues a material threat determination

In the case of COVID-19, situation three occurred. The HHS Secretary officially issued a determination of a public health emergency on February 4th, 2020. [15]

2. Next there is a Declaration of Emergency: Regarding the pandemic (on the same day as the Determination announcement), the HHS Secretary issued a Declaration that a public health emergency existed, which justified an emergency use of a COVID-19 vaccine.

3. FDA reviews EUA request: This is when the FDA Commissioner consults with the HHS Assist. Sec. for Preparedness and Response (ASPR), CDC, and National Institutes of Health (NIH) to conduct a review of the request.

4. Issuance or denial of EUA request: Upon revision of the EUA, the request may be approved or denied. At this stage in the process, all there vaccine manufacturers received approval from the FDA.

5. The last step, Termination of Declaration & EUA, is when an EUA declaration is terminated and any EUA(s) issued under that declaration will also end immediately. Basically, the HHS Secretary determines that the circumstances of the original declaration have ceased or there is a change in the approval status of the authorized product.

[As of July 19th, 2021] The public health emergency declaration for COVID-19 was originally set to expire in October 2020. HHS has renewed the declaration multiple times, including October 2, 2020, January 7, 2021, April 15, 2021, and most recently on July 19th, 2021. .[17]

Slide 35:

Now that we know how the COVID-19 vaccines were authorized, we'll discuss the technology used to develop them. The Pfizer and Moderna vaccines use messenger RNA (mRNA) technology.[18] Despite the myths and misinformation surrounding it, mRNA technology is not new. In fact, talks of using mRNA technology as a vaccine platform actually began in the early 1990s, so scientists have been researching mRNA vaccines for decades.[18] For example, in 2015 scientists who conducted early stage clinical trials of vaccines for Zika explored using mRNA. At the time, it was unsuccessful because of modest immune responses and unintended inflammatory outcomes.[18] However, recent technological advancements in RNA biology and chemistry drastically improved mRNA safety and effectiveness. These improvements have allowed for the development of the Pfizer and Moderna vaccines.

There are a few benefits associated with mRNA technology as well:[18, 19]

•It does not generate infectious particles

•It is a shorter manufacturing time compared to other types of vaccines

•And it has the potential for targeting multiple diseases with one vaccine

Slide 36:

Now, let's discuss exactly how the COVID-19 mRNA vaccines work in the body.

Here is how mRNA vaccines work:[18, 19]

1. mRNA from the virus's genetic code is injected into the patient

2. The mRNA instructs human cells to create part of the SARS-COV-2 virus called the “spike” protein. The cell gets rid of the spike protein once it breaks down the mRNA instructions.
3. Our immune system reacts to the protein (because it doesn’t belong) by producing antibodies and activating T-cells to destroy the spike proteins.
4. Lastly, the t-cells and antibodies will remember how to fight the virus, and protect you from getting sick if you are exposed in the future.

Slide 37:

Now that you have an understanding of the mRNA technology used in two of the COVID-19 vaccines, let’s briefly discuss the details of the Pfizer/BioNTech clinical trials. There were more than 40,000 participants in the Phase 3 clinical trials. 50.6% male and 49.4% female. The median age at vaccination was 51 years old.[20]

Based on FDA review, the final efficacy analysis for this vaccine was completed on Nov. 14, 2020. Overall, the vaccine proved to be 95% effective at preventing laboratory-confirmed infections of the virus that causes COVID-19 in people who received two doses.[20]

The racial and ethnic breakdown of participants in Pfizer's Phase 3 clinical trials is also depicted here. The majority of participants were White, at 81.9%. The next largest race represented was the Black/African American population at 9.8%, followed by Asian at 4.4%, then those who identified as Multiracial at 2.5%. Additionally, 73.2% of the trial's participants identified as Non-Hispanic/Latino, and 26.2% identified as Hispanic/Latino.[20]

Slide 38:

The next EUA authorized COVID-19 vaccine to become available was from Moderna. There were nearly 28,000 participants in this Phase 3 clinical trial. Breakdown based on was sex 52.6% male and 47.4% female. The median age at vaccination was 53 years old.[21]

Based on FDA review, the final efficacy analysis for this vaccine was completed on Nov. 25, 2020. Overall, the vaccine proved to be 94.1% effective at preventing laboratory-confirmed infections of the virus that causes COVID-19 in people who received two doses.[21]

The racial and ethnic breakdown of participants in Moderna's Phase 3 clinical trials is also depicted here. The majority of participants were White, at 79.4%. The next largest race represented in the study was Black/African American at 9.7%, followed by Asian at 4.7%, then Unknown at 3.1%.Additionally, 79.1% of the trial's participants identified as Non-Hispanic/Latino, and 20% identified as Hispanic/Latino.[21]

Slide 39:

Now we will discuss the third COVID-19 vaccine to receive authorization, from Johnson & Johnson.

The Johnson & Johnson COVID-19 vaccine uses Janssen’s AdVac Viral Vector Technology. The AdVac Technology is fairly new. It was first used in the Johnson & Johnson vaccine for Ebola, which was approved by the European Commission in July 2020. The AdVac vectors are made of adenovirus – a group of viruses that cause the **common cold**. These vectors are based on a modified adenovirus that cannot replicate and cause disease.[22]

Here is how the AdVac Technology works: 22

- A piece of genetic material from the SARS-COV-2 virus is placed inside of the vector. A vector then carries genetic materials into cells. In this vaccine, an adenovirus vector (which is a carrier made from a modified version of a virus that causes the common cold) from an antigen's genetic code, used to mimic the virus, is injected into the patient.
- Our immune system reacts to the antigen (because it doesn't belong) by producing antibodies and activating t-cells.
- The t-cells and antibodies will remember how to fight the virus and will prevent you from getting sick if you are exposed to the virus in the future.

Slide 40:

Now that you have an understanding of how AdVac Technology works for the Johnson & Johnson vaccine, let's review the demographic breakdown of the Phase 3 clinical trial. There were nearly 40,000 participants in the Phase 3 clinical trial. 55.5% were male, 44.5% were female, and less than 0.1% of participants identified as undifferentiated or unknown.[23] The median age at vaccination was 53 years old.

Based on FDA review, the final efficacy analysis for this vaccine was completed on Jan. 22, 2021. Overall, the vaccine is 85% effective at preventing severe disease.[23]

The racial and ethnic breakdown of participants in Johnson & Johnson's Phase 3 clinical trials is also depicted here. The majority of participants were White, at 62.1%. The next largest population represented in this phase was Black/African American at 17.2%, followed by American Indian or Alaska Native at 8.3%, and then Asian at 3.5%. Additionally, 52.4% of the trial's participants identified as Non-Hispanic and 45.1% identified as Hispanic/Latino. [23]

Slide 41:

In early April 2021, several reports of a rare blood clot condition, thrombosis with thrombocytopenia syndrome, referred to as TTS, were detected via VAERS, the Vaccine Adverse Event Reporting System. All reported cases of TTS occurred within 2 weeks of individuals receiving the J&J COVID-19 vaccine. All reported cases occurred among women ages 18 – 59 years.[24,25]

Out of an abundance of caution, the CDC and FDA recommended a temporary pause of the J&J vaccine on April 13th while experts worked to review the data. On April 23rd, after reviewing all available data, the pause was lifted by the CDC and FDA after determining that the vaccine's known and potential benefits outweigh its known and potential risks.[25]

As of July 12, 2021, more than 12.8 million doses of Johnson & Johnson's COVID-19 vaccine have been administered in the United States. Through continuous safety monitoring, 38 total cases of TTS have been identified among individuals who had received the J&J COVID-19 vaccine, the majority of whom were women between ages 18 – 59.[26]

Currently, women 50 years and younger may still receive the J&J vaccine but should be aware of this rare but adverse event risk.[26]

While media reports of the pause may have created fear and hesitancy among the general public, the J&J pause is a wonderful example of our vaccine safety monitoring systems working exactly as they should. VAERS, the system that detected the original cases of TTS, is available to medical professionals

and the general public alike, and accepts any adverse event reports following vaccination, whether they are ultimately related or not. It is a great tool to first detect any initial concerns that then may warrant further investigation, such as the reports of TTS following the J&J vaccine.

Slide 42:

Before the COVID-19 pandemic, vaccine development could take 10 years or longer from concept to approval. However, the Pfizer, Moderna, and Johnson & Johnson COVID-19 vaccines have all been developed in less than a year. How was this possible, and how do we know that these vaccines are safe?

The most significant factor in the accelerated development timelines of the COVID-19 vaccines was the significant global public health threat posed by the SARS-Cov-2 virus. As scientists discovered the virus in late 2019, and received its genetic information in January 2020, it was imperative they move quickly to provide immunization options to the public. With COVID-19 now the largest public health priority, governments and the private sector alike allocated significant funding to finding a suitable vaccine. This led to hundreds of vaccine candidates being tested simultaneously, which is not the norm. This diverse pool of vaccine candidates allowed for more options and ultimately resulted in several strong vaccines that succeeded in all phases of clinical trials.

In the United States, the federal government established enough federal funding to help develop and mobilize approved vaccines as quickly as possible to American citizens, this was known as Operation Warp Speed. To accelerate development while maintaining standards for safety and efficacy, Operation Warp Speed has been selecting the most promising countermeasure candidates and providing coordinated government support. Protocols for the demonstration of safety and efficacy were aligned, which helped allow the trials to proceed more quickly. The protocols for the trials are overseen by the federal government, as opposed to traditional public-private partnerships, in which pharmaceutical companies decide on their own protocols. Rather than eliminating steps from traditional development timelines, steps have occurred simultaneously, such as starting manufacturing of the vaccine at industrial scale well before the demonstration of vaccine efficacy and safety, as happens normally. This increases the financial risk, but not the product risk as clinical trials are not skipped, and safety data is still required to be reviewed before final authorization and release of any manufactured products.

Another factor that aided in the rapid timeline of the COVID-19 vaccines involves existing research of both other coronaviruses and mRNA technology in other vaccines.

Upon analysis of the virus' genome sequence, scientists realized that the coronavirus' genetic code was very similar to that of another coronavirus, Severe acute respiratory syndrome (SARS), which they had already encountered from the outbreak that took place in 2003. Although a SARS vaccine was never completed due to the virus's spread being contained and fizzling out, scientists had a good idea of the vaccine strategy based on previous SARS vaccine research.

Additionally, scientists had been working on developing mRNA technology to use in vaccines for over 10 years prior to COVID-19.5 Both the Pfizer/BioNTech and Moderna vaccines deliver the virus's spike protein via messenger RNA (mRNA), which is how the body's immune response is triggered. Researchers have been testing mRNA technology to develop vaccines for other viruses such as Zika, HIV, rabies, and influenza. mRNA vaccines can be developed in a laboratory using a DNA template (that can be standardized and scaled up), lending to a faster vaccine development process than traditional methods.

It is free from animal origin and synthesized without preservatives. Other benefits of using this technology includes use of a non-infectious element and the potential for targeting multiple diseases. While some may hear mRNA referred to as "new technology", it has been around for more than a decade, is familiar to researchers, and has been studied in humans outside of COVID-19 vaccine clinical trials.

Think of it as a vaccine development cheat sheet. A combination of cutting-edge technology, existing research, and funding accelerated the vaccine development timeline and FDA review process, while still ensuring vaccine safety and efficacy were achieved.

Slide 43:

Now we'll discuss some helpful resources that cover vaccine development, vaccine safety monitoring, and general information about immunizations.

Slide 44:

The first helpful resource listed is the CDC's "Vaccine Testing and the Approval Process" which outlines the development and testing processes of every vaccine. This site is a useful resource for getting an overview of the vaccine development process and links out to many more detailed sub-sections.

Next is the CDC's "Vaccine Safety Monitoring" site, which outlines how the CDC monitors vaccine safety. This site provides a high-level description of safety monitoring and also offers explanations of specific monitoring systems, such as the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

Slide 45:

The Children's Hospital of Philadelphia is a wonderful resource for all types of information related to vaccines.

Their "Making Vaccines: Process of Vaccine Development" page offers a detailed explanation of each step involved in the vaccine development process. Their "Vaccine Safety References" is a detailed library of references regarding a variety of vaccine safety-related topics and questions.

Finally, the Children's Hospital of Philadelphia's "Vaccine Education Center" is a wonderful resource for all vaccine-related topics for parents and healthcare professionals. It is vetted by the Global Advisory Committee on Vaccine Safety.

Slide 46:

Be sure to follow us on Twitter, Facebook, Instagram, and LinkedIn.

Also, if you'd like to stay updated on the latest information from The Immunization Partnership sign up for our alerts at www.immunizeusa.org.

Slide 47:

Here are the references for today's presentation.

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Slide 48:

People like you are vital in helping promote the importance about how to eliminate vaccine-preventable diseases from spreading in your communities. We hope you will take the tools, strategies, and resources you've learned about to help you understand vaccine safety. The work is ongoing as organizations like The Immunization Partnership and healthcare professionals like yourselves work to push the message that vaccines are safe and effective.

Immunize. Prevent what's preventable.

Slide 49:

If you have any questions about this presentation please reach out to Ashley Beale or Rachel Walker at The Immunization Partnership. Thank you for listening.