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A review of vaccinations: A tool in battling viral infections

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Vaccinations have historically been shown to boost a person's immune system, eliminate and prevent the spread of infections, and lessen the burden on the healthcare delivery system. In this report, we provide an overview of vaccinations and their role in combating viruses.

The concept of using vaccines has been around since the 1500s with several accounts describing smallpox inoculation as practiced in China and India.[1] The method involved grinding up smallpox scabs and blowing the matter into the nostril.[2] A vaccine is derived from the parts of a virus (antigens) that stimulate a person's immune system to produce antibodies that eventually kill the virus or prevent the disease. As a result of vaccination, the body now has a memory of the virus. If the infectious organism tries to infect the person again, the immune system will quickly recognize and remember how it fought and destroyed the virus previously.

Vaccines undergo strict testing and research under U.S. Food and Drug Administration (FDA) standards prior to becoming available to the public. Vaccinating populations has helped countries take steps toward wiping out debilitating and deadly infections such as polio and smallpox.

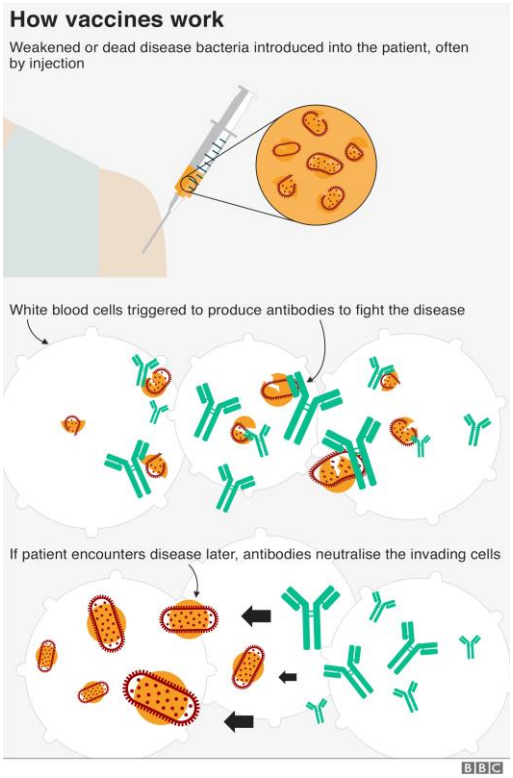
In view of the coronavirus disease (COVID-19) pandemic, this paper focuses on (1) examining why, when, and how vaccines are used, (2) highlighting the vaccine development pathway, (3) reviewing previous experience with viral pandemics, and (4) assessing ways payers can address COVID-19.

Authors' note: This paper is not meant to endorse the use or hesitancy in avoiding the use of vaccines nor does it address any controversies associated with vaccines. Due to the timing of when this article was written and rapid advances in COVID-19 data, some of the information could become outdated.

What is a viral vaccine, and why and when do we use them?

Viruses are microorganisms that are smaller than human cells. They attach to and replicate in a person's cells at an extremely fast rate.[3] Viruses produce proteins (antigens) causing the immune system to activate white blood cells (WBCs) and the production of specialized cells such as antibodies, cytokines, and B- or T-cells.[4] If the virus is new or unrecognized to the immune system, the body's response in fighting the virus can be slower. If the immune system can recognize the virus from a previous infection (or vaccine), it will activate the antibodies and quickly eliminate the virus. Vaccines have been proven to take advantage of this antigen stimulation and antibody memory activation. Vaccines may be effective for bacterial as well as viral infections.

FIGURE 1: DESCRIPTION OF HOW VACCINES WORK



Adapted from https://www.bbc.com/news/world-48186856 , Accessed March 20, 2020

The first vaccine injection was in 1796, and it was formulated using material from a cow pox virus to protect people from the smallpox disease.[5] When vaccines are administered prior to exposure to a virus, the vaccine helps the immune system create a memory of that virus so that it can quickly induce an immune response. A vaccine causes the immune system to be on the lookout for the virus by injecting pieces of the virus or the antigen, which stimulates the immune system to respond. This leads to the immune system performing its three main functions:[6]

1. Detecting unwanted or unrecognizable material produced by viruses
2. Killing or removing the virus
3. Keeping a record of the virus to reduce the likelihood of future infections

Once vaccinated, if exposed to a virus in the future, the immune system remembers the viral parts from the vaccine and recalls a quicker immune response (see Figure 1). With future antigen exposure, the antibodies and immune system will stop the viral growth, limiting the ability of it to reproduce and create havoc.[7,8,9] Not everyone has similar immune system responses. People who are immunosuppressed, have genetic mutations in their immune system, chronic diseases, or poor nutrition may have a harder time fighting viruses, which may be a reason for the lack of response to vaccines among some people.[10,11]

In recent years, most of the work done around viral vaccinations focuses on influenza (flu). Flu vaccination reduces the risk of influenza illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine.[12] In general, flu vaccines tend to work better against influenza B and influenza A (H1N1) viruses and offer lower protection against influenza A (H3N2) viruses.[13]

Vaccine approval process

In 1902, the U.S. Congress passed the first federal legislation to control the quality of drugs, the Biologics Control Act, P.L. 57-244, which focused on the manufacturing process and required that manufacturing facilities be inspected before a federal license was issued to market any "virus, therapeutic serum, toxin, antitoxin, or analogous product."[14] Since that time, other legislation has been passed to establish how vaccines are manufactured and require studies to prove safety and effectiveness under the FDA. Vaccine development and testing follows a standard set of phases (see the table in Figure 2).[15,16,17]

FIGURE 2: STANDARD FDA VACCINE DEVELOPMENT PHASES

PHASE	PHASE HIGHLIGHTS	TIMING (YEARS)*
Preclinical	A novel virus is identified. Vaccine work begins by using animals to identify: ▪ Viral antigens making a person sick ▪ Safety concerns and side effects ▪ An immune response provocation ▪ A potential human dose	1-2
I	Research starts on 20 to 80 people to assess: ▪ Safety and potential side effects ▪ An immune response by administering the vaccine along with infecting research subjects with the virus to see if the immune system will respond to the virus	1
II	Assumes Phase I trial was successful. Volunteers (100 to 300 people) will receive either the vaccine or a placebo to assess: ▪ Tolerability in people at high risk of acquiring the virus ▪ Safety and immune response ▪ Route of administration effectiveness (injected, oral, or intranasal) ▪ Number of times it can be given and dosage ▪ Ways to broadly make the vaccine	2-4
III	Assumes Phase II is successful. Phase III is a replication of Phase II on a larger group of people.	2-3
Post-approval monitoring	FDA and the Centers for Disease Control and Prevention (CDC) continue to monitor the vaccine through the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink.	None

* Assumes FDA standard review process with no government waivers on timing, simultaneous work on each phase, or collapsing of study phases from the Emergency Use Authorization (EUA) policy.

This timeline may appear to be long for developing and bringing a vaccine to the market, but it allows for the identification of key adverse events (AEs). It is critically important that, prior to administering a vaccine to millions of people, the potential risks and benefits of the vaccine are well understood, including how the immune system interacts not only with the antigen, but also with the body itself.

As with most therapies, vaccines can have AEs. There are two major AE concerns with vaccines—antibody-dependent enhancement (ADE) and cell-based enhancement (CBE). ADE of virus infection is a phenomenon in which virus-specific antibodies enhance the entry of a virus, and in some cases the replication of the virus, into monocytes/macrophages and granulocytic cells, leading to both increased infectivity and

virulence, clinically manifested by a more severe disease than in one who had not been vaccinated.[18,19,20] CBE includes inflammation caused by Th2 immunopathology in which a faulty T cell response triggers allergic inflammation.[21,22,23,24] For example, the allergic inflammation reaction was seen when researchers developed vaccines for severe acute respiratory syndrome (SARS-CoV-1), a coronavirus that was identified in 2002.[25]

While immune enhancement is a rare adverse event, if it were to occur at a rate of one per 100,000 vaccinations and 200 million people received a vaccination, then 2,000 people would experience an adverse event. Patients should be fully aware of both the benefits (immune response protecting them from the virus) and potential side effects, including severe AEs, when electing to receive a vaccine.

Viruses can experience genetic changes, known as antigenic drift. They are small changes (or mutations) in the genes of viruses that can lead to changes in the surface proteins, or antigens, of the virus. Antigens are recognized by the immune system and are capable of triggering an immune response, including production of antibodies that can block infection. The small changes associated with antigenic drift happen continually over time as the virus replicates and results in viruses that are antigenically different.[26] When antigenic drift occurs, the body's immune system may not recognize and prevent sickness caused by newer viruses. Antigenic drift is one of the reasons why it is not effective to make a vaccine for the viruses associated with the common cold and why flu vaccinations are not 100% successful.[27] In some cases, individuals may have partial immunity, from previous infection or vaccination, to infections that have undergone antigenic drift.[28,29]

Antigenic shift is an abrupt, major change in a virus, resulting in new viruses that infect human beings. Pandemics are nearly always a result of antigenic shift events. One way that a shift can happen is when a virus from an animal population gains the ability to infect humans. Such animal-origin viruses can contain an antigen combination that is so different from the same subtype in human beings that most people do not have immunity to the new (e.g., novel) virus. When this shift happens, most people have little or no immunity against the new virus.

Presently, we do not know enough about the SARS-CoV-2 virus to know the impact of antigenic drift and antigenic shift on the effectiveness of a vaccine for COVID-19 in future years. With this in mind, a conservative approach of continuous surveillance might be reasonable, similar to how the influenza vaccine is updated yearly.

Under special considerations, the government could waive some of the development timeframes under the FDA Emergency Use Authorization (EUA) policy in order to address the critical need for vaccines against novel viruses like COVID-19. A Phase I clinical trial evaluating an investigational vaccine designed to protect against COVID-19 started in March 2020, but at the time of this publication, no other vaccines have moved out of the preclinical phase.[30,31] Estimates are that it could take 12 to 24 months before an approved vaccine for COVID-19 will be available to the market.[32] This 12 to 24 months is a compressed timeline, outside of the FDA standard timing. Consideration to move the process along more quickly, such as allowing certain aspects of the development process (Phase III) to proceed simultaneously without the earlier phases being completed (Phase II), may need to be addressed. The federal government would likely need to implement an EUA for these studies in order to meet this compressed timeframe, and on May 15, 2020, the White House announced Operation Warp Speed, a public-private partnership to develop and manufacture hundreds of millions of COVID-19 vaccine doses by January 2021.[33] Consumers need to know that, as of the date of this paper, there are no FDA-approved COVID-19 vaccines. Some private entities are trying to take advantage of consumer fears and confusion, selling unproven COVID-19 treatments.[34] The FDA is aware of these false claims and has issued warnings to entities promoting COVID-19 treatments and vaccines.

In summary, the process of FDA approval requires the vaccine to demonstrate two vital concepts: (1) efficacy, so it contains the right viral antigens producing an antibody response, and (2) safety, so that the frequency of adverse events is low. These concepts are of concern as earlier trials with vaccines for SARS-CoV-1 have not shown a favorable risk-benefit profile. While a COVID-19 vaccine may not be available in a short-term timeframe, it is likely that with the resources being invested, one can be hopeful there will be a significant scientific breakthrough for a treatment and a vaccine against COVID-19.

How much do we know about viral infections?

A viral pandemic is characterized by (1) person-to-person transmission sustained over a period of time, (2) an increased death rate, and (3) worldwide spread.[35] The largest viral pandemics we have experienced are related to the influenza virus and human coronaviruses (HCoVs). Some of the characteristics and experiences with these viruses are described below.

HUMAN CORONAVIRUS OUTBREAKS

HCoVs are common and typically cause a variety of mild to moderate respiratory tract infections. However, different strains can spread rapidly and cause more severe symptoms with more severe HCoV strains, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) viruses.

A global outbreak in 2003 of the SARS-CoV-1 lasted nine months and resulted in over 8,000 people infected and over 700 deaths, though few in the United States.[36,37] The case fatality rate was 11% and the transmission period was six to 11 days.[38,39] Currently, no vaccine is available for SARS-CoV-1.

The MERS had a global outbreak in 2012, with more than 2,400 cases reported to the World Health Organization (WHO) and more than 850 deaths.[40,41,42] The case fatality rate was 34%, which means that over three out of every 10 people who contracted MERS died.[43] Most people who died had preexisting medical conditions that weakened their immune systems or had underlying medical conditions.[44,45] Few deaths were reported in the United States.[46] No vaccine exists for MERS.

Containment of SARS and MERS was possible because these viruses had rapid onset and high mortality. Consequently, as the infected person was not in the community and unable to transmit it to another person, these viruses "burned themselves out." Containment was also aided with surveillance, prompt isolation of patients, and strict quarantine enforcement.

The more recently identified SARS-CoV-2 virus is what causes the COVID-19 disease. COVID-19's serial interval, meaning the time between successive cases, is close to or shorter than its median incubation period, suggesting that presymptomatic transmission plays a key role in the outbreak, and that case isolation alone might not be as effective as hoped. The characteristic rapid onset seen with other HCoVs is not seen with COVID-19, which has an asymptomatic preclinical phase, leading to it spreading efficiently and slowly in communities and higher incidence rates.[47,48]

It is believed that the COVID-19, SARS, MERS, avian influenza (bird flu), and swine influenza viruses first circulated in infected animals (zoonotic) and then became harmful to humans.[49] While these types of viruses are acquired by direct contact with infected animals or contaminated environments, with the exception of COVID-19, they do not spread quickly between people. If a virus acquires the capacity to spread sustainably from one person to another, as with COVID-19, it has the potential to lead to a pandemic because human beings would have little immunity to a new virus. Thus, while researchers might leverage their knowledge of the zoonotic virus, the development of a vaccine takes time.

INFLUENZA OUTBREAKS

Several strains of influenza have contributed to four pandemics in the past 100 years-- in 1918, 1957, 1968, and 2009 (see the table in Figure 3). The deadliest pandemic was the 1918 Spanish flu (H1N1), which contributed to a lowering of the average life expectancy by 12 years in the United States. Spanish flu killed much more quickly, spread slowly, and had rapid onset of symptoms. In the 1918 influenza pandemic, there were no surveillance, monitoring, or vaccination programs to help lessen its effect on the population.[50]

In 1957, a new influenza A virus (H2N2) emerged triggering a pandemic known as the Asian flu. An estimated 1.1 million individuals worldwide, including 116,000 in the United States, died from the H2N2 pandemic.[51] With the exception of persons over 70 years of age, the public was confronted with a virus with which it had had no experience.[52]

The 1968 pandemic was caused by an influenza A (H3N2) virus. An estimated 1 million worldwide and about 100,000 in the United States died from the H3N2 pandemic.[53] A significant number of deaths were of people 65 years and older. The H3N2 virus continues to be present across the world as a seasonal influenza A virus and, as it undergoes regular antigenic drift, it continues to be associated with severe illness in older people.[54]

FIGURE 3: SELECTED VIRUS PANDEMICS[55,56,57,58,59,60]

	SELECTED INFLUENZA VIRUSES		HUMAN CORONAVIRUS (HCOVS)		
Highlights	1918[61,62]	H1N1 (2009)[63,64,65,66]	COVID-19[67,68,69] (±)	SARS[70,71]	MERS[72,73]
Worldwide deaths	50 million	575,400	356,606	916	>850
Who was at riskα	15-34 years of age	Children, young and middle-aged adults	High-risk conditions	High-risk conditions	High-risk conditions
Symptom onset (days)	Rapid	1-4	11.5	2-7	5-7
Incubation (days)	Unknown	1-4 days	2-14	5	5
Serial interval	Unknown	2.6 days	4-7.5	8.4	6.8
Vaccine	None	Available	None	None	None

α Excludes people with other illnesses; however, others could contract the virus.

± As of May 16, 2020.

Note: High-risk conditions include diabetes, immune suppressed, frail and elderly, chronic lung disease, chronic kidney disease, liver disease, and serious heart conditions.

A novel influenza A (H1N1) virus emerged in 2009, which contained a unique combination of influenza genes not previously identified that were not included in the seasonal flu vaccine. It was a deadly virus for those at risk, children, and young and middle-aged adults. It is likely that one-third of people 60 years of age and older had antibodies to this virus from earlier exposure in their lives. While a vaccine was produced, it was not widely available during the peak infection time.[74]

HOW ARE INFLUENZA AND COVID-19 SIMILAR AND DIFFERENT?

Both influenza and COVID-19 appear to cause respiratory disease with a wide range of presentations from asymptomatic to death. As many as 25% of people infected with COVID-19 are asymptomatic.[75] Upwards of 80% of patients who contract COVID-19 develop only mild flu-like symptoms.[76] While the mortality rate for influenza is estimated to be 0.1%, at this time the exact rate for COVID-19 is unknown, with estimates from 0.28% to 3.4%.[77,78] Both influenza and COVID-19 viruses are transmitted by contact, droplets, and fomites. Current research supports the possibility that COVID-19 could be spread via bioaerosols generated directly by patients' exhalation, which are fine particles emitted when someone breathes. These can be suspended in the air, rather than with larger droplets, which are produced through coughs and sneezes.[79] The median incubation period for influenza is three to five days and it is estimated to be four to five days for COVID-19.[80,81] Proper and meticulous hand and respiratory hygiene, along with avoidance of symptomatic individuals, are important measures that a person can take to control viral spread. Influenza and COVID-19 have unique differences regarding when it is contagious, what population it is likely to affect, and how deadly it can be.

Payer considerations for providing coverage related to COVID-19

A number of initiatives that payers may consider to enhance access and lessen the member burden related to COVID-19 are identified below. This is by no means an exhaustive list, as payers recognize that members, regardless of a COVID-19 diagnosis, still need routine and emergency access to healthcare. Each organization will need to assess the practicality and legality of these initiatives on an individual basis.[82] These initiatives include:

- Waiving patient share of costs for COVID-19 diagnosis and treatment
- Waiving hospital, provider, and pharmacy out-of-network rules
- Payment for telephone and telehealth interactions at parity with payment for office visits
- Implementing telehealth and home delivery for diagnostics and drug therapies
- Coverage of remote monitoring technologies for chronic conditions under medical and/or pharmacy benefits
- Allowing pharmacists to provide 30-day emergency refills of prescriptions under certain conditions
- Allowing pharmacists to order and administer COVID-19 tests
- Offering medication therapy management (MTM) services to all members
- Proactive identification of medication alternatives for patients in case of drug shortages
- Suspending prior authorizations
- Moving to notification-only requirements for inpatient and outpatient care services
- Delaying medical necessity reviews of inpatient and subacute services
- Offering mobile medical care to ease the burden on medical providers and the emergency department
- Crisis meal deliveries

Conclusion

A person’s immune system is the primary defense against viral pathogens like COVID-19. We are yet to have an effective treatment or vaccine to prevent its spread. Because asymptomatic people can spread the virus to others, avoidance (also known as social distancing), wearing masks, and meticulous hand washing appear to help with decreasing the spread of COVID-19. Ultimately, vaccination may be the best tool to prevent the future impact of COVID-19, but it could take time to bring a COVID-19 vaccine to market. Anticipating the future availability of a COVID-19 vaccine, stakeholders should address questions now, including prioritizing who should get the vaccine, administration and distribution, and how a vaccine will be covered and reimbursed.

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ENDNOTES

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