Commentary ISSN 2694-5614

Journal of Pharmaceutical Research and Development

An Interview with Dr. Manuel F. Varela: Conquered Microbes

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Submitted : 18 Jan 2022 ; Published : 2 Feb 2022

Citation: Shaughnessy, M. F., & Varela, M. F. An Interview with Dr. Manuel F. Varela: Conquered Microbes. J Pharma Res Dev, 2022, 3(1): 1-8.

Dr. Varela, we are currently coping with this COVID virus—but I want to trace a history of infectious diseases—and those viruses and bacteria that we have conquered—to give people some insight into the process.

So—I will name a virus or a bacterium, you tell us about it—and then give us a brief history as to how it was conquered.

Polio

Polio is an illness caused by the microbe called poliovirus. For millennia, the human populace feared the disease, often called infantile paralysis due to early-onset after birth. New advances in the science of polio treatment, microbiology, and vaccine biology became possible with the March of Dimes fundraising. In modern times, the disease is virtually eliminated in the Western Hemisphere and may soon be eradicated from the planet, thanks mainly to the success of the polio vaccination programs.

Patients with poliovirus infections experience wide ranges in disease severity, from an asymptomatic condition, minor illness, to major illnesses, the latter of which can be severe with total paralysis of the body. The degree of disease severity is dependent on several factors, such as the viral serotype, the amount of viral dosage, location of the infection in the body, the point of viral entry into the patient, and the patient's age and health status.

The microbe, a virus, has an RNA genome surrounded by a protein shell called a capsid. Poliovirus comes in three varieties: Types 1, 2, and 3, which are dictated by the nature of the antigens on the microbe. The polioviruses are transmitted to people by the oral-fecal route, characterized by poor hygiene, diapers in daycare units, food or water contaminated with sewage, handling of contaminated objects, or even by inhalation of virus. Before the advent of the vaccines, the primary treatment method for paralytic polio was the iron lung, Figure 1, which worked by pressuring the lungs to contract and expand to permit patients to live artificially. Today, iron lungs are primarily relegated to museums.

Figure 1: Children with paralytic polio in iron lungs. https://commons.wikimedia.org/wiki/File:Iron_Lung_ward-Rancho_Los_Amigos_Hospital.gif

There are two primary poliovirus vaccines: the Salk and the Sabin vaccines. An inactivated virus characterizes the Salk vaccine, developed by Jonas Salk. Called IPV for inactivated poliovirus, the Salk vaccine is administered by injection. The Sabin vaccine, developed by Albert Sabin, is a live virus but attenuated and taken orally. The Sabin vaccine is also called OPV, for oral polio vaccine. Both of these vaccines can target the three types of poliovirus. They provide effective adaptive immunity to the poliovirus by eliciting protective antibodies.

The prevention of polio disease onset by IPV and OPV represents one of the major triumphs of modern science. In the late 1970s, polio cases due to poliovirus disappeared from the U.S. The eradication of polio disease on a global scale is tantalizingly near, with worldwide cases numbering very low. However, a few pockets of the paralytic form of poliovirus exist in locales where vaccination is lacking. If vaccination programs were permitted to proceed in such areas, poliomyelitis could be eradicated from the Earth.

Tetanus

Tetanus manifests itself as an involuntary muscle contraction condition. It is considered a dreadful disease because victims can suffer slow, painful suffocation before death. If the patient survives by some miracle, long-lasting effects may include a

broken back due to intense back muscle contractions. If all of a patient's muscles contract simultaneously, the dire situation is called opisthotonos. Figure 2 shows a classic painting by Charles Bell of a Napoleonic soldier with war wounds dying of tetanus on the battlefield.

Figure 2: A tetanus patient with opisthotonos, painting by Charles Bell.
https://commons.wikimedia.org/wiki/File:Opisthotonus_in_a_patient_suffering_from_tetanus_-_Painting_by_Sir_Charles_Bell_-_1809.jpg

Tetanus is acquired by transmitting a bacterium called *Clostridium tetani* to the patient by trauma to the skin in which endospores enter wounds, undergo vegetation, and release a potent toxin. The tetanus toxin prevents the relaxation of contracted muscles, producing lockjaw, spasms, and in severe cases, opisthotonos, resulting in painful slow death by suffocation. Sometimes treatment involves surgical debridement in which affected tissues are removed, and in rare cases, amputation may be indicated.

Thanks to vaccine-induced immunity, tetanus is now rare in the U.S. However, the incidence of tetanus, unfortunately, remains much higher in regions where vaccination is not practiced. The vaccine is protective and consists of a denatured tetanus toxin called a toxoid.

Measles

Measles, or rubeola, is a highly infectious viral disease. Figure 3 shows a pediatric patient with measles. The ailment is one of the most contagious, and the clinical illness is characterized by fever, cough, fear of light, a rash covering the body, and the formation of so-called Koplik spots, which are lesions that appear on mucous membranes.

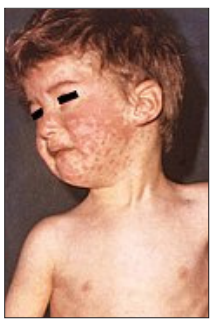

Figure 3: A child with measles.
https://commons.wikimedia.org/wiki/File:Boy_with_measles.jpg

The measles virus's causative microbe is from the Paramyxoviridae family's genus *Morbillivirus*. The mature virion consists of an antisense single-stranded RNA genome enclosed in a nucleoprotein capsid and covered by a membrane-based envelope consisting of a lipid cell membrane, often stolen from the cell that the virus had infected. The mode of measles transmission to patients is airborne by inhalation of large respiratory droplets containing the infectious virion.

The protective vaccine consists of a live attenuated version of the microbe in which the virus is non-pathogenic but effectively antigenic, meaning that immunity is conferred to the vaccinated individual. Once considered a common childhood disease, measles is now rare in developing nations due to vaccinations. Before implementing a new vaccination program, the incidence in the U.S. was 300 cases per 100,000 in 1981. After introducing the measles vaccine, the incidence fell to 1.3 cases per 100,000 in 1988. A 99.5% reduction in cases was recorded between the pre-vaccination era in 1955 and the more current post-vaccination time. In regions without vaccination programs, epidemics of measles continue to occur. Worldwide, measles deaths number in the hundreds of thousands annually, with over 10 million cases per year.

Mumps

Like measles, mumps is another highly communicable disease caused by a Paramyxoviridae family member of the *Paramyxovirus* genus or simply the mumps virus. The mumps virus genome is a negative-sense single-stranded RNA molecule covered by a nucleocapsid and an envelope. The mode of measles transmission is via breathing of virus-harboring respiratory droplets. Like measles, much of the pathology of the mumps virus is immune system-based, involving inflammation by the innate immunity component of the body's immune system. However, much of the ultimate recovery is based on the cell-mediated branch of the patient's immune system.

The pathology of mumps involves infection of the patients' respiratory tract cells, with the viruses spreading into the blood, a condition called viremia. Sometimes, the viruses can spread to other body parts, like the parotid glands, the testes, and the brain and spinal cord. The patient can experience parotitis, a painful swelling of the saliva glands in the cheeks.

The mumps vaccine is a live attenuated virion that is nonpathological but highly immunogenic, generating a lifelong protective form of cellular immunity to the disease. Without vaccination programs, about 90% of that population acquires mumps by 15 years. Starting in the late 1960s with the new vaccination program in the U.S., the mumps incidence rate was 76 cases per 100,000 people, culminating in less than one case per 100,000 until the advent of the recent so-called anti-vax movement. For example, in 2014, an outbreak of mumps occurred in Ohio with over 230 new cases. Currently, no antiviral medicines for mumps are available.

Rubella

Previously known as the German measles, rubella is another childhood disease characterized by a rash and swollen glands. The infecting microbe is a virion of the *Rubivirus* genus, previously belonging to the Togaviridae family of viruses, now a member of the Matonaviridae family. The Rubella virus has a positive sense-stranded RNA genome, a surrounding nucleocapsid, and an envelope cover.

Transmission of the virus occurs via inhaling large respiratory droplets containing the small virus. While the disease is considered benign, severe congenital disabilities can occasionally occur when pregnant women have an infected fetus. Congenital rubella syndrome is characterized by the onset of eye cataracts, skin lesions, heart defects, hearing loss, severe mental impairment, failure to thrive, and death by one year after birth, Figure 4. Currently, no treatments for rubella are available.

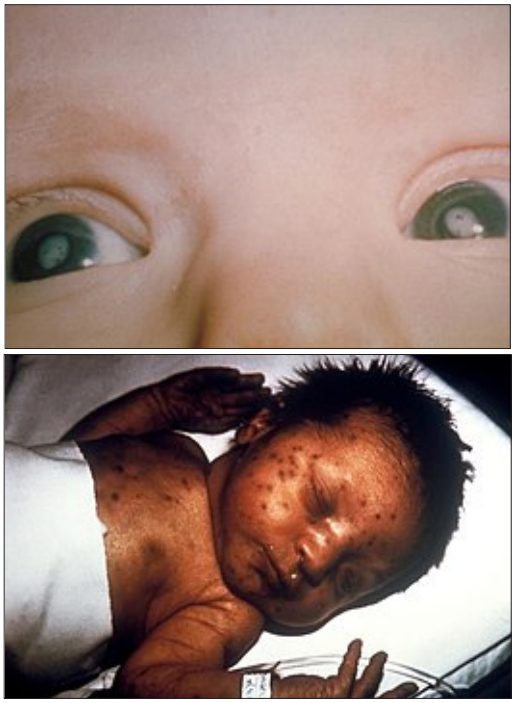

Figure 4: A child with cataracts and an infant with skin lesions have congenital rubella.

https://commons.wikimedia.org/wiki/File:Cataracts_due_to_Congenital_Rubella_Syndrome_(CRS)_PHIL_4284_lores.jpg
https://upload.wikimedia.org/wikipedia/commons/7/7a/Infant_with_skin_lesions_from_congenital_rubella.jpg

A successful immunization program was started in the U.S. in the mid-1960s, culminating in almost complete eradication of rubella cases in the early 1980s. The vaccine consists of a live strain of the virus called RA27/3. The rubella vaccine is provided as one component of the trivalent MMR vaccine for measles, mumps, and rubella. The MMR vaccine confers both effective humoral and cellular immunity. MMR is typically administered by injection at one year of age and represents one of the crowning achievements in disease prevention in the U.S.

Chickenpox

Caused by the varicella-zoster virus (VZV), the chickenpox infection is characterized by fever and a series of progressive skin lesions called the maculopapular rash. The chickenpox disease is transmitted by inhaling respiratory droplets harboring VZV and directly contacting afflicted patients. Chickenpox is considered highly contagious, especially in children who are not immune, serving as a continual source of the virus. Consequently, the virus can be continually present in such populations in areas lacking vaccination.

The VZV microbe is a member of the Herpesviridae family, with a DNA genome surrounded by a protein capsid and an envelope membrane. In particular, the VZV enjoys infecting nervous tissue, and when recovery from chickenpox occurs, the neurons are often harbingers of latent varicella-zoster viruses. In some cases, the latent VZ virions can reactivate, producing a long-lasting painful shingles condition in the elderly and patients immunocompromised by stress.

Treatment of shingles can involve nucleoside analogs as antiviral agents like acyclovir, which inhibit DNA synthesis by targeting host DNA polymerase enzymes. However, such antiviral treatment is not always satisfactory if given late during the disease course, in which case pain killers can provide some relief.

Prevention is achieved by a live attenuated varicella-zoster viral vaccine, producing protective antibodies and cell-mediated immunity. For children, the vaccine is called Oka, and in adults, it is referred to as zoster. A newer vaccine, called Shingrix, is based on a VZV sub-unit component called glycoprotein E.

Influenza

Influenza disease has wreaked such tremendous havoc amongst human populations for centuries with periodic pandemics that the microbe was named the influenza virus for its deadly influence. One of the deadliest of these pandemics occurred in 1918 and 1919, in which an estimated 20 to 50 million people perished. Due to this historic pandemic, the lessons learned included early testing, patient quarantine, isolation of close contacts, and the wearing of face coverings. See Figure 5.

Figure 5: Women are donning surgical face masks during the influenza epidemic, Brisbane, 1919. https://commons.wikimedia.org/wiki/File:StateLibQld_1_104332_Women_wearing_surgical_masks_during_the_influenza_epidemic,_Brisbane,_1919.jpg

In the years since, tens of thousands of influenza-caused deaths have occurred in several more recent flu pandemics. The classic signs and symptoms of influenza disease include fever, headache, malaise (uneasiness and discomfort), and soreness in the muscles. Other signs and symptoms include chills, loss of appetite, runny or stuffy nose, sore throat, and a non-productive cough. Without complications, recovery can occur in seven to ten days. However, death can occur at a mortality rate of 40% from complications like pneumonia (lung inflammation) and secondary bacterial infections.

The microbe contains eight (+)-sense single-stranded RNA molecules in its core, with ribonucleoprotein protecting the RNA genome enclosed underneath a matrix protein (called M1) layer and a lipid-based envelope. See Figure 6. Emerging from the matrix-envelope structure are two types of spikes, the hemagglutinin (HA) and the neuraminidase (NA) molecules, which have sugars attached, forming so-called glycoproteins. The HA spike is attached to host cells, and it permits viral cellular entry by fusion. Once inside the cell, M2 protein allows unpackaging of the viral genome by pumping protons into the enclosed virus. Meanwhile, NA facilitates the escape of the newly formed influenza virus from infected cells. Packaged inside the core are loose molecules for making genomes (RNA polymerase) and NS1 and NS2 to process and assemble the virus inside host cells.

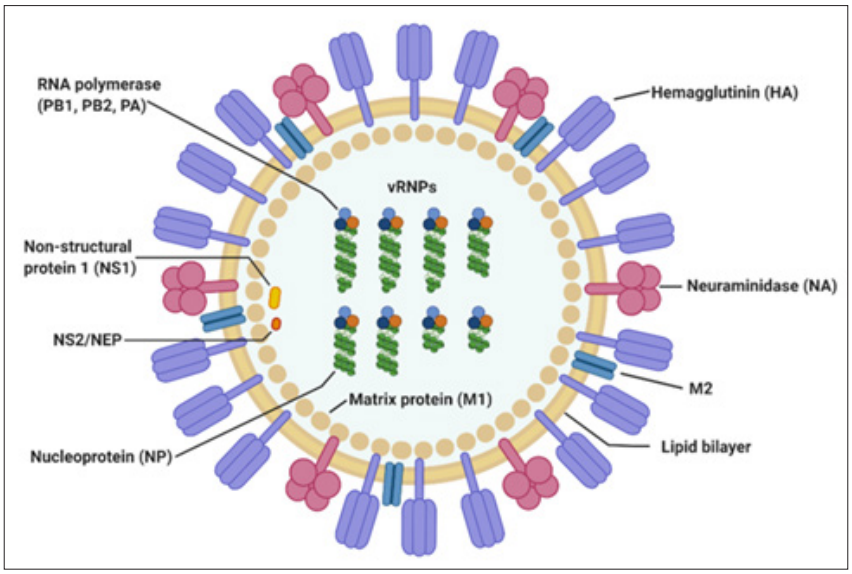

Figure 6: Structure of influenza virus. https://commons.wikimedia.org/wiki/File:Viruses-12-00504-g001.webp

Since the genome of the influenza virus is RNA, the microbe is prone to mutation because the synthesis of RNA is more frequently inaccurate. Hence, the flu microbe can mutate into more infectious variants, similar to the case with the RNA genome of SARS-CoV-2, the causative agent of COVID-19, in which problematic viral variants have emerged. The influenza virus can mutate ever so slightly, causing antigenic drifts. These variants can be predicted and addressed by designing new vaccines each year. However, occasionally, the microbe can significantly alter its genome, causing antigenic shifts, characterized by recombination or reassortment of genomic RNAs, the variants of which can be unpredictable and cause concern because of their potential to cause pandemics. Due to antigenic shifting in the virus, such flu pandemics have been documented in 1918, 1947, 1957, 1968, 1977, 1997, 2003, and 2009.

While antiviral agents are available as medicines in severe clinical cases, vaccine-based prevention is preferred to avoid hospitalization costs and suffering from the disease with the risk of death. A similar strategy of prevention by vaccination is sought after by medical and biomedical experts regarding COIVD-19. There are several primary flu vaccines. The inactivated subunit influenza vaccine contains a mixture of HA and NA proteins that are purified or in extracts from the viral strains grown in embryonated chicken eggs. The so-called killed flu vaccine consists of isolated influenza viruses inactivated by formalin, causing the virions to lose pathology but keep immunogenicity to generate an immune response. A live but attenuated viral flu vaccine is available as a nasal spray for children who fear needles. It is well documented that flu vaccination programs significantly reduce disease incidence, hospitalizations, and deaths.

Hepatitis A

Hepatitis A virus, a (+)-sense single-stranded RNA virion belonging to the genus *Hepatovirus* and member of the Picornaviridae family, causes infectious hepatitis. The genome is covered by a capsid that selectively adheres to the human liver cells. The microbe is transmitted by the fecal-oral route when victims consume food or water contaminated with fecal matter harboring the viruses. While often mild, infectious hepatitis can cause significant case numbers in outbreaks from food consumption and water contaminated with sewage and daycare centers from mishandling dirty diapers.

Signs and symptoms of infectious hepatitis include fever, nausea, vomiting, tiredness, appetite loss, and pain in the abdomen. Later signs and symptoms include jaundice, dark urine (bilirubinuria), pale stools, and abdominal pain.

Prevention measures against outbreaks include public sanitation, proper food handling practices, and washing hands between patients and diaper changing. A hepatitis A vaccine is available and consists of a killed viral preparation administered in two injections spaced six months apart.

Hepatitis B

Serum hepatitis is caused by the microbe called hepatitis B virus. Unlike hepatitis A, the hepatitis B microbe has a circular DNA genome and an envelope. The mature hepatitis B virion structure contains packaged molecules for nucleic acid replication and protein kinase for encouraging the liver infection process. The virion also harbors surface antigens that permit binding to liver cells.

The modes of transmission for hepatitis B include contact with blood products through contaminated needles, tattooing, ear piercings, and sexual contact or viral passage through the placenta from a pregnant mother to the fetus.

Epidemiologically speaking, the mortality rates per year are staggering, with about 5,000 yearly deaths in the U.S. alone. It has been approximated that more than 12 million Americans have had hepatitis B infections. Worldwide, over 350 million cases of serum hepatitis B have been recorded, with about one million deaths occurring per year. The World Health Organization has estimated that most liver cancer cases are due to the hepatitis B virus.

Considering these gloomy statistics is surprising because infectious hepatitis B and liver cancer cases are preventable with vaccines. One hepatitis B vaccine is based on the so-called HBsAg viral-like particle. A more recent vaccine is a genetically engineered version where a plasmid specifies assembly of the HBsAg, which is combined with alum as an adjuvant to enhance immunity potency. A newer vaccine, called Heplisav-B, is composed of HBsAg and molecules of cytosine phosphorothioate guanosine oligodeoxynucleotide, another useful potent adjuvant.

Diphtheria

Diphtheria is a toxin-mediated bacterial illness. The disease is present in many areas of the world but is relatively uncommon in the U.S., thanks mainly to a vaccine. For example, in 1921, the U.S. suffered from approximately 200,000 cases, but only two American cases have been reported since 2003. In areas of the world where no active immunization programs exist, diphtheria outbreaks are known to occur.

The causative agent, a bacterium called *Corynebacterium diphtheriae*, produces a virulence factor that generates the signs and symptoms of its illnesses. Its two forms, respiratory and cutaneous, characterize the disease. Both forms involve the formation of a thick pseudomembrane, a material that covers the initial site of infection. The pseudomembrane is tissue combined with bacteria, immune cells, fibrous material, and dead cells. The pseudomembrane can occasionally block the airway and breathing in respiratory diphtheria. Sometimes, complications can arise involving the heart or nervous system, producing more severe illnesses and deadly outcomes. In cutaneous diphtheria, the pseudomembrane takes the form of a grayish-colored membrane on the skin and may involve additional complications like a secondary bacterial infection.

An important issue concerning diphtheria is early treatment, characterized by diphtheria antitoxin. If the antitoxin is not administered early on during the disease onset, antibiotics are indicated. After recovery, immunization with the diphtheria toxoid is necessary as a natural infection is typically insufficient to provide immunity to the illness.

As noted above, diphtheria is preventable. A vaccine exists where the toxin itself is denatured into a safe toxoid form but effectively immunogenic. Immunization programs are in place in the U.S. to provide the diphtheria toxoid vaccine as three-part preparation, called DPT, for diphtheria-pertussis-tetanus. The term DTaP (or sometimes Tdap) is used for diphtheria-tetanus-acellular pertussis. Pertussis disease is also known as whooping cough (see below), and tetanus was discussed above. DPT is administered in five injections at 2, 4, 6, 15, and 18 years of age. Then, a booster of diphtheria and tetanus is given every ten years. DTaP is given after seven years.

Hib

The term Hib is a colloquial expression to denote the vaccine of *Haemophilus influenzae* type B, the bacterium that causes various illnesses such as meningitis, epiglottitis, pneumonia, sinus infections, ear infections, cellulitis, and bacteremia, to name a few.

Incidentally, the name *Haemophilus influenzae* had arisen out of the then mistaken notion that it caused the flu. These bacteria do not cause the flu. Influenza virus causes the flu. However, investigators erroneously thought the bacterium did cause influenza at some point in its history because the specimens from flu patients inadvertently also harbored the bacteria as non-causative contaminants.

Interestingly, *Haemophilus influenzae* enjoys blood meals, and when provided in culture media in Petri dishes, the bacteria will eagerly destroy the blood using a variety of hemolysins, proteins that break apart red blood cells. Furthermore, the bacterium is present as an unencapsulated form in virtually all human beings, as we carry it in our mouths, throats, and other regions of the upper airway. However, in rare cases, *Haemophilus influenzae* can be enclosed by a protective capsule, an encapsulated version, that promotes virulence and disease because the immune system is thwarted by the capsule.

Nevertheless, a vaccine has been responsible for effectively protecting most individuals in the U.S. and represents an astonishing success of immunization programs. Before the vaccine was introduced, approximately 20,000 cases of infection occurred each year in the U.S., mainly in children. After a massive immunization program was started in the late 1980s, the incidence of infection in children under age 5 diminished almost entirely. In 2015, only about two dozen cases were reported.

One of the vaccines, Hib, is composed of a capsular polysaccharide-protein conjugated to each other. The capsular component of the conjugate is called PRP, for polyribitol phosphate, a type of sugar. The Hib vaccine promotes effective antibody production and function, which involves clearance of the virulent bacterium from the body. A newer vaccine variant is composed of a conjugate between the *Haemophilus influenzae* B polysaccharide from the capsule and the diphtheria toxoid protein.

Whooping Cough

Also known as pertussis, the whooping cough illness manifests as a set of paroxysms, a series of repetitive coughs in which the patient's lungs empty out, followed by a loud inspiratory "whooping" sound as the patient attempts to inspire air back into their lungs. The ailment can last two to four weeks, at which time convalescence can occur unless complications like secondary bacterial infection set in. The disease is often more severe in infants and young children than in adults.

The infectious disease is transmitted by inhaling bacteria-laden aerosols from other coughing patients. The causative agent, a tiny bacterium called *Bordetella pertussis*, has no known place to live except in the airway of humans. In populations where no vaccination programs are present, the microbe enjoys wide distribution from person to person via their respiratory routes. The tiny size of the bacterium permits its facilitated entry into the lungs of unsuspecting victims. Unvaccinated individuals are most at risk for acquiring the illness and experiencing severe courses of disease.

The *Bordetella pertussis* bacterium produces a series of virulence factors, which allow the microbe to avoid the immune system, attach to cells of the airway, and, in the case of the pertussis toxin, produce a massive respiratory secretion of mucous, leading to the classic whooping cough stage. The virulence factor called tracheal cytotoxin inhibits an innate immunity component of the immune system by preventing the sweeping action of cilia, thus, preventing clearance of the bacteria from the airway. Three of the cell-binding virulence factors made by the bacteria are called pertactin, filamentous hemagglutinin, and fimbria.

Treatment of whooping cough clinical disease involves a course of antibiotics such as azithromycin, erythromycin, or clarithromycin, all of which fall into the macrolide class of antimicrobial agents. Prevention can be established by the administration of the so-called acellular pertussis vaccine. The term acellular refers to the fact that the vaccines do not contain intact microbes. They contain only inactivated bacterial components and not infectious agents. There are two acellular pertussis vaccines, one for children and the other for adults. Both vaccines harbor denatured pertussis toxin (which is unable to elicit disease), plus pertactin and the filamentous hemagglutinin.

The pediatric pertussis vaccine is provided in five doses, beginning with the first three doses at 2, 4, and 6 months, and the fourth vaccine dose between 15 and 18 months, plus the fifth pertussis vaccine dose between 4 and 6 years. Older children can be vaccinated with the adult pertussis vaccine at

11 and 12 years, and adults between 19 and 65 years. The great majority of the deaths, numbering around 160,000 per year worldwide, are unvaccinated children.

Rotavirus

Rotavirus causes a cholera-like type of diarrhea called gastroenteritis and can be serious if present in young children. However, infants are most at risk for the condition known as human infantile gastroenteritis. Fever, vomiting, and dehydration frequently accompany diarrhea. The illness that is caused by rotavirus is spread between patients by a fecal-oral route of transmission, and it is, thus, quite contagious. For a patient to acquire the illness, a requirement is that the victim must consume fecal matter from a person who has the illness, even if the patient is asymptomatic. The virus can survive on dry and wet surfaces and on the hands of patients.

Rotavirus microbe takes its name from the wheel-like appearance of the mature virion, see Figure 7. The rotavirus is a member of the so-called Reoviridae family. The family name is derived from an acronym REO, which stands for respiratory-enteric-orphan viruses. The term "orphan" stems from the happenstance that it was first discovered without a known disease with which to attribute. Today, we know that the reoviruses cause a variety of infections. The rotavirus itself is characterized by an unusual double-stranded RNA genome! The rotavirus genome is segmented, meaning that it occurs in several pieces, between 10 and 12 molecules, depending on the strain. The ds RNA genome molecules are surrounded by a double layer of capsid proteins, providing a protective shell for the viral genome.

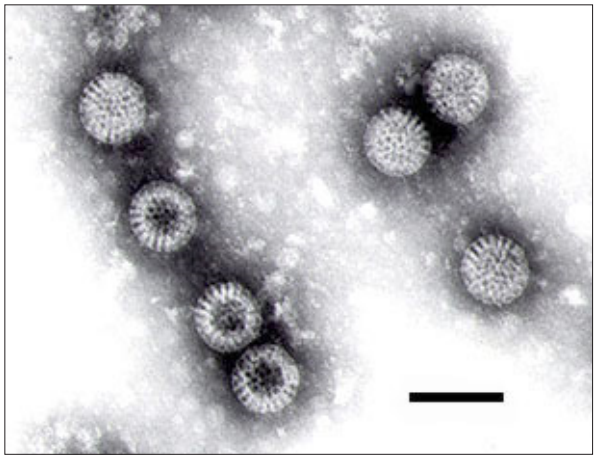

Figure 7: Rotaviruses, as seen with the electron microscope, with its wheel-like structure.
https://upload.wikimedia.org/wikipedia/commons/f/f7/Rotavirus.jpg

Treatment of diarrhea by rotavirus involves rehydration, providing lost water and electrolytes. Control of rotavirus illness involves proper hygiene practices and handwashing after diaper changing and bowel movements. Prevention entails a live oral vaccine in which doses are administered at 2, 4, and 6 months. One developed rotavirus vaccine, called RotaTeq, consists of five reassorted strains specific for cows. Another rotavirus vaccine called Rotarix contains a single strain of the human-specific virus. Both of these rotavirus vaccines are well documented to be safe and effective.

Before rotavirus vaccines were available, approximately 500,000 to 1 million deaths occurred every year, most occurring in infants. In the U.S., four of every five children have suffered from rotavirus-mediated diarrhea. In contrast, in areas of the U.S. where the vaccine is provided, the incidences are rare. Not surprisingly, rotavirus is endemic in regions worldwide where vaccination programs are not followed.

Pneumococcal Disease

Pneumococcal disease is caused by the respiratory-laden bacterium called *Streptococcus pneumoniae*. Its origins in scientific history date back to the time of Louis Pasteur, who isolated the microbe in his laboratory, calling the microorganism Microbe *Septicemique du salive*, but George Sternberg, who also found it, had named the organism as *Micrococcus pasteuri.* In the early 20th century, the scientific name was changed to *Diplococcus pneumoniae* before becoming known by its extant name, *Streptococcus pneumoniae*, in 1974.

Two forms of the bacterium exist. One strain lacks a protective capsule and is, hence, relatively harmless, as the human immune system can effectively purge the microbes from the body. On the other hand, the virulent strain harbors the protective capsule, permitting it to circumvent the immune system and cause serious and potentially fatal diseases. Once the immune system is evaded, other virulence factors come into play, permitting the bacteria to colonize, spread, and stimulate the body's inflammatory response.

The microbe causes not only pneumonia but also meningitis, sinusitis, otitis media, and bacteremia. The pneumococcal disease develops into pneumonia when the bacteria are inhaled into the respiratory system, depositing in the tiny alveolar spaces of the lungs, where the microbes can multiply rapidly. The microbes cause so-called lobar pneumonia when they are aspirated into the lower regions of the lungs. Frequently, the coughing is accompanied by severe chest pain when the linings of the lungs experience inflammation, a condition which is called pleurisy.

Unfortunately, despite the availability of a vaccine, the pneumococcal disease remains a leading cause of infection and death. The pneumococcal vaccine is based on purified components of the capsule cover, which, when administered to individuals, provides protective immunity.

Smallpox

Of all the illnesses discussed here, smallpox represents the prime example of an astonishing triumph by human intervention towards the global eradication of a disease—smallpox. Known by its historical name for the two variants *Variola major* and *Variola minor*, the scientific name of the microbe has the genus *Orthopoxvirus* belonging to the Poxviridae family. The smallpox virus had been the bane of human infection for

millennia, with fearsome periodic outbreaks wreaking havoc as it moved through human populations until its eradiation from the planet in the late 1970s. The disease is characterized in severe cases by grotesque lesions throughout the body and accompanied by high fever, headaches, achy muscles, malaise, and tiredness. Occasionally, the patient experiences bleeding, diarrhea, and vomiting. If the patient survives, lifelong immunity is almost assured.

The causative agent of smallpox is a very large virion harboring a DNA genome and enclosed by an envelope. The respiratory route of transmission acquires the illness, and it moves through the body using its lymphatic system and ending with viremia, the presence of the virus in a patient's blood.

The smallpox vaccine dates back to ancient times with the advent of variolation, a method practiced by the Chinese in which dried material from a smallpox lesion was inoculated into a healthy individual, providing immunity to the illness. In the late 1700s, the British surgeon Edward Jenner took advantage of the cross-reactivity of cowpox immunity to vaccinate individuals and protect against smallpox. Jenner had used cowpox vesicular material from a dairy milkmaid patient named Sarah Nelmes and injected it into a child named James Phipps. Young Phipps then survived a high dose of smallpox-laden material afterward, demonstrating the efficacy of cowpox as a vaccine against smallpox. Cotton Mather adopted the vaccination method in the early American colonies. In modern times, the vaccine consists of a live vaccinia virus preparation but is reserved primarily for individuals in the military. Naturally occurring cases of smallpox disappeared after an intensive vaccination program was initiated during the 1960s. Except for a few laboratory accidents resulting in deaths, no natural smallpox cases have been recorded since 1977 when Ali Maalin, the last known patient in Earth's history, had been diagnosed.

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