Drugs and Beyond

Virus and Vaccination

HPPS Journal Issue 4:

Introduction to Viral Infection and Vaccination

Interesting articles including The Big Five, Antivirals, Anti-Vaxxers and Vaccines in Development

Meet the expert: Frank van Kuppeveld

News including the Awareness Calendar, Latest News and Internships

Dear HPPS Communitiy,

Welcome to this fourth issue of Drugs and Beyond! Ever since the summer holidays, we have been working hard on writing articles about a new topic for you to delve into: Viruses and Vaccination. We will take you on a journey through subjects, including a general introduction to viral infection and the 'Big Five' viruses at the moment, as well as how viruses evolve over time. This will be followed by the history of vaccination, the anti-vaxxers discussion and vaccines in development. We will then let you know something about antivirals and cancer vaccines too. Considering the current corona-crisis, an update regarding this subject will be given as well.

As always, we will provide you with new updates about the HPPS community. Which projects are running and recruiting currently? What kinds of internships are being carried out by members? What is going on at the university, and what exactly are they building at the David de Wied building? Besides that, we have the usual content that has been spread out over the journal, such as internships, more details on several awareness days and an interview with a researcher. Lastly, we have added some new topics that will be coming back in the following issues, namely a meme page and 'Diseases that Have Led to a Medical Breakthrough'.

We hope that you enjoy this issue, and that you will join us for the next issue that will come out after the summer holiday!

The Drugs and Beyond team:
Hanneke, Jaap, Jacqueline, Jamie, Kyra, Mirthe, Nina, Sanne and Yvonne

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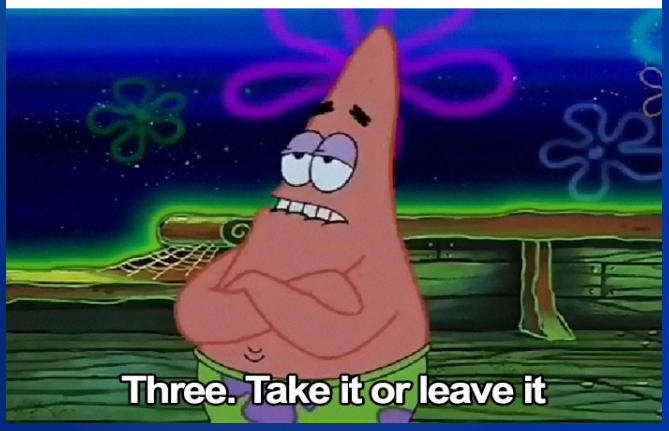

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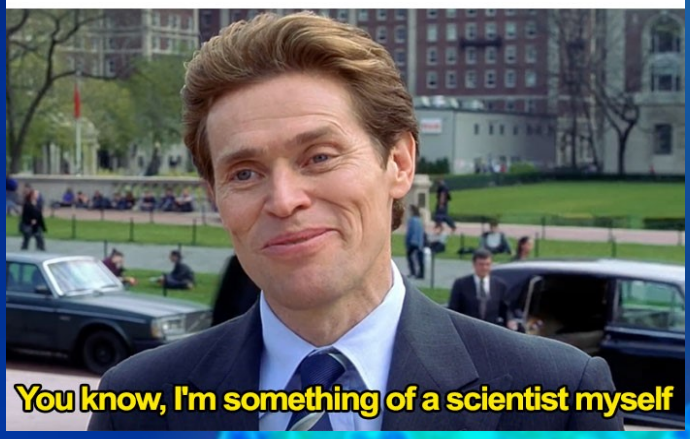

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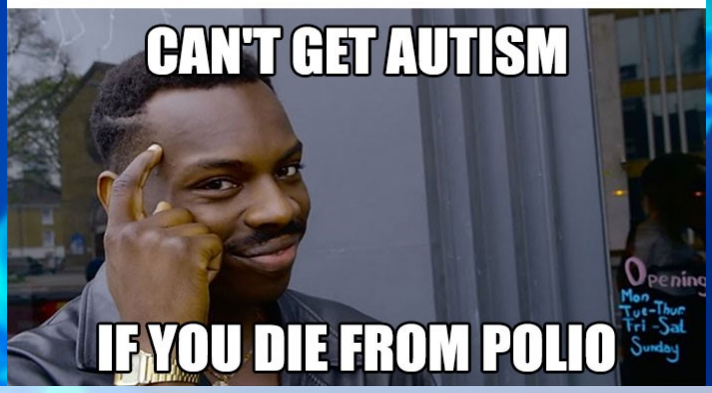


Introduction to Viral Infection

Viral infection, also called viral disease or infectious disease, is caused by viruses that invade host cells to reproduce and thereby cause disease that can greatly impact the host's health. To better understand the mechanism behind this phenomenon, a closer look is needed.

The virus is a small particle containing genetic material, which can be DNA or RNA and single stranded or double stranded. Some viruses contain material that encodes 4 proteins, while others can encode up to 200 proteins. This nucleic acid is encapsulated by a protein shell, which can have various shapes and sizes and plays a protective role. Together they are referred to as the nucleocapsid. Some viruses also have a lipid envelope, which consists of a lipid bilayer of host cell lipids and contains virally encoded proteins. These proteins help with the host cell receptor binding, membrane fusion, and cell-entry. The entire intact virus particle is called a virion.[4]

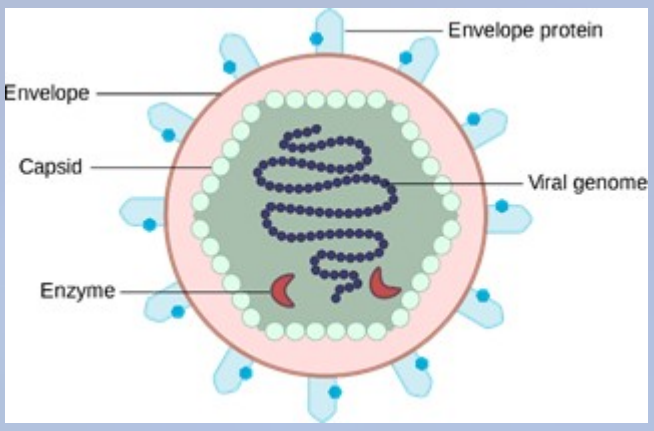


Figure 1: The virion [5]

One important aspect of viruses is that they cannot reproduce by themselves. Thus, a host cell is needed for their reproduction. They will enter the cell and direct it to produce more and more viruses. That cell is now infected. The immune system of the host will respond and try to destroy and remove the virus particles and infected cells, which in many cases damages vital tissues. [4]

Transferred into the host, either by an animal vector such as a mosquito or directly by for example inhalation of virus particles, the virus will try to enter a cell by attaching to a specific receptor site on the membrane, using the proteins on the capsid and the lipid envelope. If the particle is able to attach, it either injects the genetic material in the cell leaving the capsid and envelope behind or enters the cell through endocytosis. When using endocytosis, the membrane will engulf the virion entirely. Inside the cell, the nucleic acid will be released by degrading the capsid either with the help of viral or host enzymes or by simple dissociation. DNA will enter the nucleus, while RNA will stay in the cytoplasm. The virus will now start its reproduction. Most families will first direct the host cell to transcribe the genetic material into viral mRNA and then translate the mRNA to viral proteins. Other families that contain RNA as their nucleic acid, first translate the RNA to form viral proteins. These proteins consist of polymerases, which in their turn transcribe the RNA to produce more mRNA. In total, there are 7 pathways of viral nucleic acid replication, depending on the type of nucleic acid. In all cases, the host cells are directed to transcribe the mRNA to form the viral proteins, which also consist of the structural proteins that form the capsid. Last part of the replication is the multiplication of the genome. This is achieved using early or regulatory protein expression. Enveloped viruses are then assembled at the plasma membrane, from which it uses budding to leave the cell, as can be seen in step 5 of Figure 2. Most non-enveloped viruses leave the cell using cell lysis. The new virions can then infect another cell by extracellular dissemination or cell-to-cell spread, where the virions will not enter the extracellular environment. An advantage of this pathway is that the host defense mechanisms will be avoided. [6][9]

The host defense mechanisms recognize the viral proteins as foreign and respond with a humoral and cellular immune response. The former focuses on the virus particles in the extracellular environment, while the latter tries to destroy and remove the infected cells. With the humoral response, B lymphocytes produce antibodies that neutralize the viral particles by binding to the capsid or envelope proteins. This prevents the attachment and entry to the cell. The complement system is also activated by the antibodies and helps defend the host by phagocytizing the virus or coating the particle.

However, this type of immunity only works when the virus has yet to enter the cell. If it is already inside and has thereby infected a cell, the cellular immune response comes into play. The cellular immune response kills infected cells using cytotoxic T-cells.

The infected cells display MHC class I molecules to let the immune system know they are infected. The cytotoxic T-cells can then induce apoptosis and stop the infection using their specific T-cell receptors. However, viruses are highly adaptable, and some are able to stop cells from presenting the MHC molecules. Fortunately, NK cells can detect cells that have less MHC molecules presented and will kill them using a similar mechanism as the cytotoxic T-cells. Also, the infected cells are able to produce interferons that will hinder the viral replication and warn neighboring cells, which will then present more MHC molecules so it will be more visible to the cytotoxic T-cells in the case of an infection.[7][8] The cytotoxic T-cells frequently kill important cells such as neurons, muscle cells, and liver cells as well as induce an inflammatory response, which can cause tissue damage. The immune response can therefore also cause (chronic) symptoms. Most chronic viral diseases are even a result of this.[7]

A chronic infection, such as chronic hepatitis C, has a continued presence of the infection. Next to these chronic viral infections, there are local and systemic acute viral infections, that both occur almost directly after the invasion of the host cell and at the site of the infection. It is also possible that an infection shows without symptoms. This type of viral infection, also named latent, does not affect the cells they have infected. The virus can stay dormant for months or even years, before it finally breaks through. This is the case with herpes viruses. Finally, a slowly progressing infection is characterized by its long incubation period, which develops into a progressive disease. The measles virus is such a virus with a long incubation period. It can take up to 10 years before a progressive disease is present. Herpes, chronic hepatitis C, and measles viruses are not the only well-known viral infections.[9] Many have impacted our society greatly and are present in a large part of the population. Even though many vaccines have been developed, many viral diseases are still untreatable.

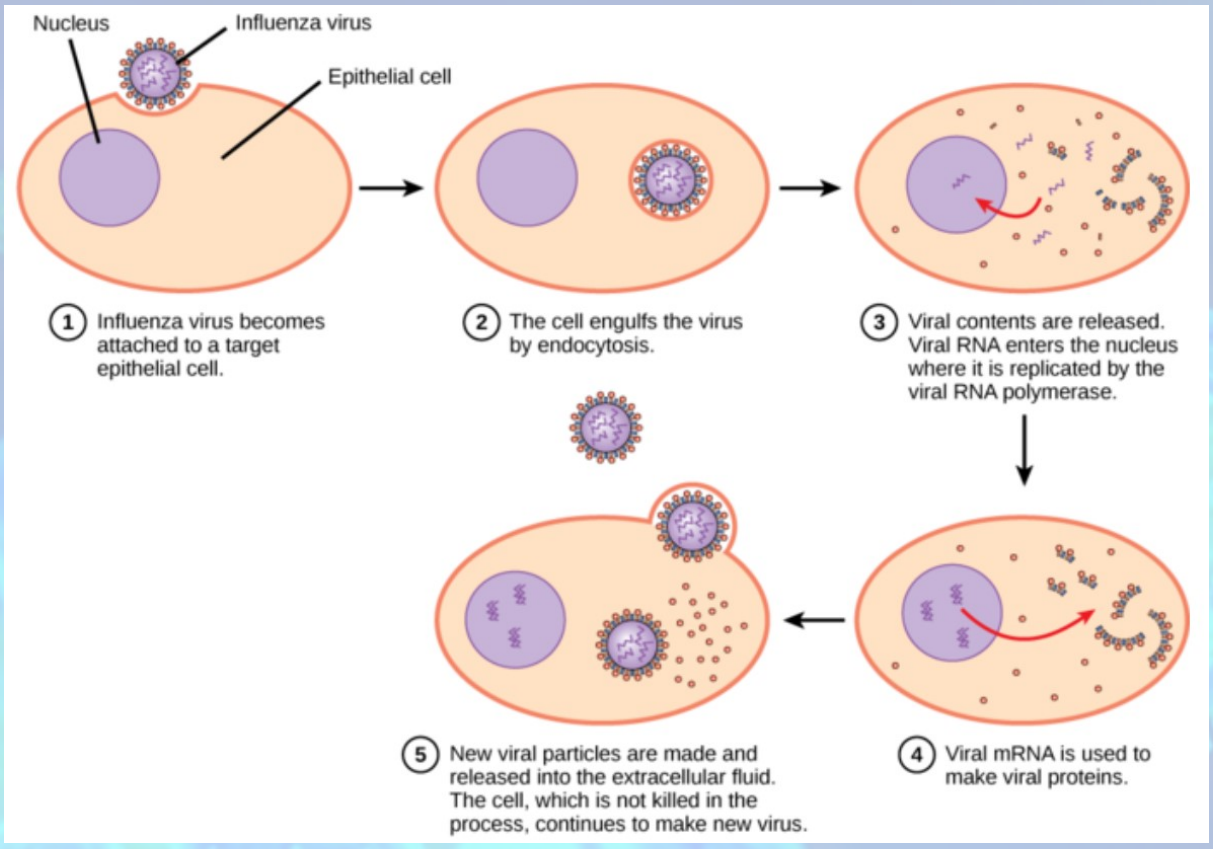


Figure 2: The infection pathway of the influenza virus [6]

The Big Five

Influenza, Herpes, Polio, Alpha Viruses and HIV

There are many viruses that infect humans, some can be fought off quite easily but others can do serious harm [10]. Many viruses are deadly and quite common, especially in the developing world. But also in the developed world viruses are a serious risk to our health. Here we have chosen to elaborate on five big viruses that have serious consequences for humans: influenza - better known as the flu, herpes, polio, the alpha virus family and HIV.

Influenza

Influenza is really common and when flu season occurs approximately 500 000 people die worldwide. However, there are many types of influenza, that keep mutating and also occur in other mammals, such as our livestock [11]. Influenza B only infects humans and spreads widely, while influenza A is seen in other animals. It is rare for humans to get infected by influenza A, but it does happen, mostly from birds, and our bodies are not used to these influenza strains. Then there is the case of flu pandemics, the biggest one being in 1918 with the Spanish flu. Here approximately 50 million people died worldwide, after 40% of the population got infected [10]. It is mostly dangerous for risk populations, such as infants, elderly and people with a chronic disease [12].

Influenza's Mechanism and Seriousness

The influenza virus has a single strand of negative-sense RNA coding for seven to eight segments that code 11 genes [12, 13]. Three of these genes give the virus its often spherical form, with a lipid bilayer with 3 proteins. Then there is a matrix protein that holds the RNA strand wound around holding proteins and its polymerase complex. One of the proteins in the lipid bilayer is hemagglutinin (HA), which can bind sialic acid in host cells to enter and fuse with the cell [13]. The virus infects the epithelial cells in the respiratory system, both in the upper and/or the lower part. Infection in the lower part has a worse prognosis for survival in risk populations [12]. The distinction between type A and B is mostly due to the HA protein, as the protein in type B can only recognize □(2,6) linkage, while the avian type A recognizes □(2,3) linkage and can therefore normally not infect human cells [13]. Swine cells have both linkages and can therefore be infected by both types, where mutations may occur that change the linkage type. After connection to the host cell the virus is taken up in an endosome by receptor-mediated endocytosis. The low pH in the endosome enables the virion to fuse with the endosome membrane and release the RNA and its transcription system into the cytoplasm. The RNA has proteins with nuclear localization signals that can bind to the nucleus' own import system to be imported. The RNA needs to be a positive sense to be translated, and the viral RNA does not have the 5' cap that human RNA has. The virus snatches the mechanism that caps the human RNA to do it and also uses the human splicing mechanism to splice its RNA. Furthermore, it blocks the cells splicing mechanism to splice host mRNA by binding to it and relocalizing it to the nucleus, where it cannot function. This gives the problem for the host cells as they cannot function properly anymore. When everything is replicated and translated the particles travel to the cell membrane and form new virions to infect other cells [13].

The body's immune system should recognize influenza viruses upon a second infection, however the virus mutates very quickly within each 'life' cycle, as it has no repair mechanism for mutations [12]. The beneficially mutated viruses keep infecting people again, and are not immediately recognized by the immune system. Therefore the body takes longer to fight the infection, and the virus has already affected many cells, and has been spread to other people. These fast mutations make the virus so dangerous, as the risk populations' immune system is impaired, and every infection is seen as a new one. The effect the virus has on the respiratory tract can by then, already be lethal [12].

Herpes

Herpes is an infection caused by the Herpes simplex viruses (HSV). There are two types, Human alphaherpesvirus 1 and Human alphaherpesvirus 2. Type 1 infects oral cavities, while type 2 infects the genitals [14].

The virus can be spread through bodily fluids, such as saliva, sperm or vaginal and anal discharge, as it is present on the skin and can be transferred with the moist. The symptoms of an infection include pain, changed discharge, redness of the skin, blisters and ulcerations. This might go together with a slight fever. There is no cure for the virus, and the only medication that can be given are antivirals. The virus is most often transferred just before, during and just after visible blisters, but even when there are no symptoms it might be transferred [14]. In the US approximately 50-67% of people are thought to be infected with type 1, but not everyone experiences an actual outbreak, and 15-20% are thought to be infected with type 2 [14, 15].

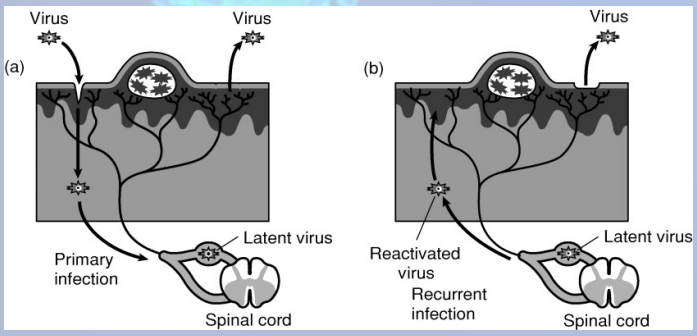


Figure 3: Primary infection of the Herpes simplex virus on the left, and recurrent infection on the right [16]

In Figure 3 the infection mechanism of the HSV can be seen. The virus penetrates the skin through a wound or a mucosal surface and then creates blisters and lesions [16]. The more severe the primary infection, the bigger the chance that the virus will nestle in the dorsal root ganglia after replication to create a latent virus, which can be reactivated to create recurrent infection. The severity is seen as the amount of lesions and their size. A trigger, such as an impaired immune system due to stress or illness, can create a flare up. HSV can also cause inflammation in the eyes: keratitis, and inflammation in the brain: encephalitis [16]. In keratitis the cornea of the eye gets infected and may be red and painful [17]. HSV can cause scarring of the cornea or even blindness [17].

Herpes is a special virus, as not many can infect and replicate in the central nervous system (CNS) [16]. This is special as neuronal cells do not produce cellular DNA due to being terminally differentiated. The virus also needs to go post-synaptically to the dorsal root ganglia, which is a cluster of neurons near the dorsal root of the spinal nerve [18]. They therefore need proteins that can enter the correct membranes. The infection of the brain has serious consequences. The first symptoms are often mild, like the flu (e.g. headache, fatigue, fever, muscle pain), but can become very severe, including seizures, hallucinations, paralysis and loss of consciousness [19]. As HSV can be latent, a secondary inflammation, for example in the brain, can happen at any moment. Approximately 70% of patients with encephalitis die without correct treatment [16].

Polio

Poliomyelitis is the disease that results from an infection with the Polio virus, however not all infected people get symptoms [20]. 1 in 4 infected get flu-like symptoms, such as nausea, fever and a headache but some people might also get meningitis, which is an infection in the brain and/or spinal cord; paresthesia, which feels like getting pricked in the legs with needles; and weakness in the limbs or even paralysis. In the case of paralysis the person actually has polio as a disease, otherwise it is just the infection. A polio vaccine has been developed, and in the developed countries it is often part of the standard vaccination program for children, as the disease mostly hits children younger than 5 years old [20, 21, 22]. In the Netherlands the vaccine has parts of the three different polio strains, and due to the vaccination programme the disease does not occur anymore in the Netherlands [21]. However, in some countries the disease is still active, despite the worldwide vaccination initiative [22].

The virus spreads person-to-person through feces, which may contaminate water sources [20]. A person can get infected when touching objects or people that have had contact with contaminated feces, and then eating without decontaminating their hands. Since the vaccination programme that started in 1988 the disease prevalence has decreased with 99%, as there were previously 350 000 cases per year [22]. From the three wild strains type 2 has been eradicated, but the other two strains could give up to 200 000 new cases if more people stop vaccinating their children [22].

Alpha viruses

The alpha-virus genus includes multiple viruses, namely the Chikungunya virus, the Semliki Forest virus and the Sindbis virus [23]. The viruses can infect both animals and humans and can be transmitted by mosquitoes and other arthropods, and are therefore called arboviruses [23]. None of these viruses are lethal without an already compromised immune system, but they do cause flu-like symptoms and both the Chikungunya and Sindbis virus cause joint pains that can persist for months or even years after infection [24, 25, 26]. There are no vaccines or antivirals available to treat these infections, they can only be prevented, which means preventing mosquito bites. The incubation time from bite to symptom appearance seems to be approximately 7 days but much is still unknown about these viruses. Infection cannot occur from person to person (only by blood transfusions), but only indirectly by mosquitoes. While the virus is replicating a mosquito can pick it up and infect others with it, and during August and September most infections occur.

Mosquito borne infections are the biggest cause for human diseases carried by vectors [27]. Due to global warming the regions in which mosquito species thrive are rapidly changing, and the diseases they carry with them also spread [28]. Together with our population density and international and intercontinental travels increasing, these diseases expand their regions faster than ever before. Not only the alphavirus burden will increase over time, but also that of many other infections carried by mosquitoes, and without treatments they can become more and more threatening [28].

HIV

The Human Immunodeficiency Virus (HIV) seems to originate in the Democratic Republic of Congo, where it spread from chimpanzees to humans around 1920 [29]. Before 1980 there were no actual records of people having HIV or developing the active disease Acquired Immune Deficiency Syndrome (AIDS) but the epidemic seems to have started in the mid 1970s. In 1981 the first cases of a severe immune deficiency appeared in the US in gay men that died of other diseases and in 1982 it was seen as a sexually transmittable disease and called 'gay-related immune deficiency'. Later that year the disease was named AIDS and in 1983 it was also found in females, suggesting it was not only transmitted by male-male sex, but also male-female sex. The virus itself was named HIV in 1986 and a year later the first drug, zidovudine, was approved as a treatment for HIV [29]. There are millions of people infected with HIV and the number keeps rising with people having unprotected sex with multiple people. This is a big problem in the developing world where both condoms and the current treatments are not widely available. Without treatment the infection leads to worsening AIDS over time and people are very susceptible to other diseases, as their immune system is not working properly. In 2013 35 million people were thought to be living with HIV and by 2017 a record of 19.5 million were on antiretrovirals, slowing the disease progression towards AIDS [29]. 21% of people are estimated to be living with HIV without knowing, causing more infections worldwide [30].

The virus is thought to come from the Simian Immunodeficiency virus (SIV) from chimpanzees as well as from sooty mangabeys [31]. There are several strains of HIV, HIV-2 comes from the sooty mangabeys but is not that infectious, while there are four HIV-1 strains, similar to the chimpanzee SIV. HIV-1 M is the most common strain and is spread worldwide, the others are N, O and P. The 4 HIV-1 types come from chimpanzees and are thought to have spread to humans by eating the meat or blood coming into cuts during hunting, and that is why there are four types [31]. HIV infects the T-helper (CD4+) cells that normally help regulate the immune system [32]. By replicating in these cells the immune system gets damaged and more virions get free to infect more cells. Normally the T-helper cells help fight off infections and protect against cancer, and some of the first cases recognized died of cancer [29, 33]. HIV infection can take up to 10 years to become AIDS, while the immune system becomes weaker and weaker, and it is diagnosed as AIDS when there are less than 200 CD4+ T-cells/mm^3 in the blood or there is an opportunistic infection, which occurs more often in immune compromised people [33].

Virus Evolution

In our current world almost all living species carry viruses that can specifically infect that species, and some may be able to cross over from one species to another. But where did those viruses originate? Just as we can only take educated guesses about the origin of all forms of life, we also only have hypotheses about the origin of viruses [34].

There are three main hypotheses for this: the progressive hypothesis, the regressive hypothesis and the virus-first hypothesis. The first, the progressive hypothesis states that viruses come from mobile genetic elements, called retrotransposons, that acquired the ability to cross from cell to cell. Retrotransposons are pieces of RNA that could be made into DNA by reverse transcriptase and ligated into the DNA of the cell. This is similar to what happens in the replication cycle of a current retrovirus, which might illustrate this hypothesis. The retrotransposons are also a component of eukaryotic genomes [34].

The second hypothesis, the regressive hypothesis, states that viruses come from more complex forms of life that over time lost essential genes. Some viruses are bigger and have many more genes than others, so viruses might have originated from more complex forms of life. Experts think that the lifeforms once lived together in symbiosis, but that one organism started to depend more on the other, turning parasitic and losing genetic material in the process, needing the other lifeform to survive and becoming a virus [34].

The last hypothesis is the virus-first hypothesis, which says that viruses existed before cells did. This would mean that the viruses could self-replicate, maybe by the enzymatic activity of some RNA (ribozymes) and formed more and more complex structures which later formed a cell wall and became cells. The viruses then learned to infect the new cells and co-evolved with them. There is no certain proof for any of these theories, so none, or all, may be true, as there could have been multiple paths for the origins of different viruses, as there are so many different ones [34].

Like explained previously in the influenza piece of 'The Big Five', viruses mutate quickly and can therefore evolve and undergo natural selection. When two viruses infect a cell at the same time they can mix and become a new virus and as there are no RNA repair mechanisms, mutations are acquired quickly. That is why we often have a cold or the flu every winter season, when our immune systems are a little bit weaker [35]. This is also how HIV can acquire resistance to the drugs used to stop its progression. When people do not take their drugs according to the guidelines, some viruses might be able to mutate in a way that the drug cannot affect them anymore, making it ineffective [35].

As viruses have coexisted with all species and can sometimes crossover between species this variability becomes a big problem. Often, like with rabies, the virus can cross from a dog or monkey to a person, but cannot be transferred from person to person without contact of blood. When a virus is introduced from another species and can spread from person to person, every subject of that species can become ill. They have never encountered that virus before and do not have immunity, creating epidemics or even pandemics. This is what happened with many SARS viruses, like the current COVID-19 and the previous ones in the early 2000s [36].

Most viruses are not deadly as that would not be useful for their own survival, they are often only lethal to people or animals with a compromised immune system. Currently with our intercontinental travel and huge population, the spreading of a virus is very easy. There is an evolutionary way viruses survived without killing entire populations or separate settlements in epidemics [37]. As the people lived in small groups separated from each other there were no new incomers that brought foreign viruses with them. If there was a newcomer with a virus either everyone died or a few got ill and the others became immune. Both resulted in no new people to infect and the virus would die.

Viruses mutated to survive and could become latent, they would infect one generation, lay low for a while, and when new children were born, infect that generation again as these children were new susceptible hosts. This can be seen from the measles outbreaks in Iceland. After infection people either die or become immune, but only those who encountered the virus. After a new generation was not immune and someone from overseas brought the virus with them a new epidemic would start the cycle again as these people were not immune [38]. In chickenpox children become ill from the varicella-zoster virus and they often become immune, however the disease nestles and stays in the nerves. When the immune system weakens in one's 60s to 80s the nestled virus might give rashes that can spread the virus again to susceptible children. Viruses need new people to infect regularly, or the virus stops replicating in that population. Nowadays there are enough new susceptible hosts after a new or mutated virus appears with all the intercontinental travel, and without drugs or vaccination programmes it could be a disaster.

Awareness Calender

September 2019:

- **Usher Syndrome Awareness Day (Sept. 21)**
- World Sepsis Day (Sept. 13)
- World Rabies Day (Sept. 28)
- World Heart Day (Sept. 29)

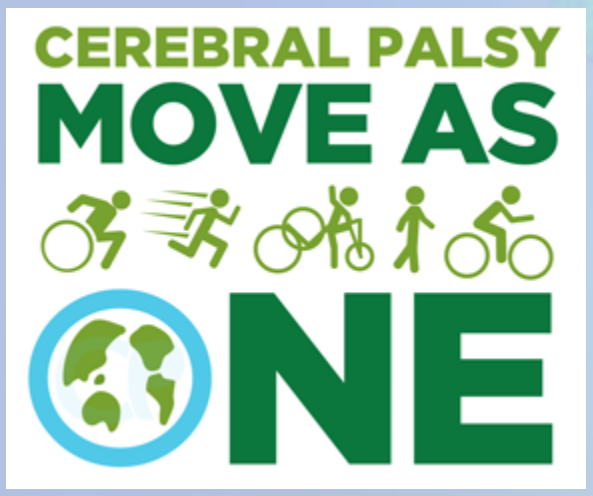
Usher Syndrome Awareness day (Sept. 21 2019)

In 2015, the Usher Syndrome Coalition declared the third Saturday in September the global "Usher Syndrome Awareness Day." The chosen day is close to the fall equinox in the northern hemisphere, marking the start of days that contain more darkness than light - a powerful metaphor for the threat of Usher syndrome. [39]

Usher syndrome is the most common genetic cause of combined deafness and blindness. More than 400,000 people are affected by this disease worldwide, which impacts three major senses in the body: vision, hearing and balance. The vision loss in Usher Syndrome is caused by a process called retinitis pigmentosa (RP), in which the light-sensing cells in the retina gradually deteriorate. This results in night blindness, followed by tunnel vision as the disease worsens. Hearing impairment in children with Usher Syndrome is either congenital or developed due to the condition. Lastly, people with Usher Syndrome suffer from severe balance issues because of dysfunction in the vestibular organs in the inner ear. [40] [39]

October 2019

- Spina Bifida Awareness Month
- Sudden Infant Death Syndrome (SIDS) Awareness Month
- **World Cerebral Palsy Day (Oct. 6)**



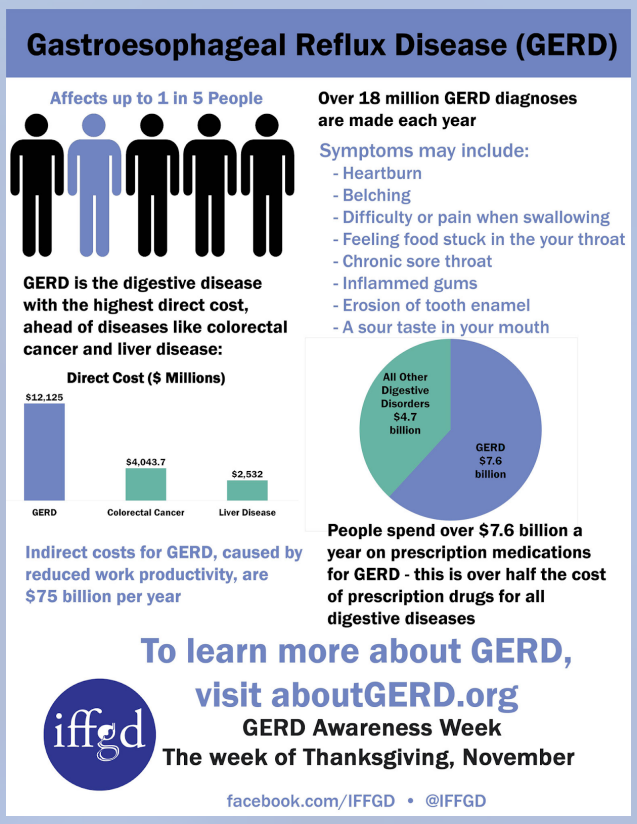
World Cerebral Palsy Day (Oct. 6 2019)

World Cerebral Palsy Day is organised in more than 75 countries by a movement of people with Cerebral Palsy and their families, and the organisations that support them. Their vision is to ensure that people with Cerebral Palsy (CP) have the same rights and opportunities as anyone else in society. Across the world, there are 17 million people living with CP and nother 350 million people are closely connected to a child or adult with CP.

CP is the most common physical disability in childhood, with permanent effects on the motor system. The impact can range from a weakness in one hand to almost a complete lack of voluntary movement. Symptoms include, but are not limited to, talking impairment, inability to walk, intellectual disabilities and epilepsy. [41]

November 2019

- World Prematurity Day (Nov. 17)
- Great American Smokeout (Nov. 21)
- International Survivors of Suicide Day (Nov. 23)
- **GERD Awareness Week (Nov. 24–30)**
- World Antibiotic Awareness Week (TBA)



GERD Awareness Week (Nov. 24-30 2019)
Gastroesophageal reflux disease, or GERD, is a very common disorder. Each year around the week of Thanksgiving, the International Foundation for Gastrointestinal Disorders encourages people experiencing the symptoms, displayed on the poster and which may be GERD-related, to consult their physicians and to contact them to receive information and support regarding the condition.[42]

GERD affects up to 1 in 5 or more of adult men and women in the U.S. population. Although common, the disease often goes unrecognized, which is unfortunate because GERD is generally a treatable disease, but serious complications can result if it is not treated properly.

Heartburn is the most frequent, but not the only symptom of GERD, as it is often characterized by many painful symptoms that can undermine an individual's quality of life. GERD is often unrecognized or misdiagnosed as heartburn is not specific to GERD and can result from other disorders that occur inside and outside the esophagus. Furthermore, GERD is a chronic disease. Treatment usually has to be maintained on a long-term basis, even after symptoms have been brought under control. Various methods to effectively treat GERD range from lifestyle measures to the use of medication or surgical procedures.[43]

December 2019

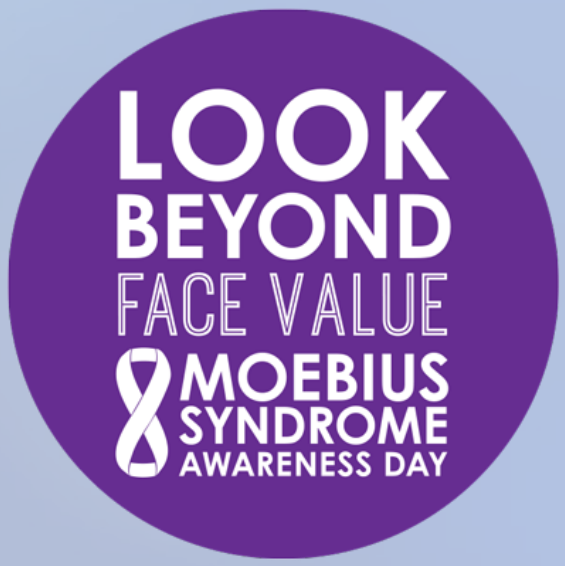
- World AIDS Day (Dec. 1) (was done last issue)
- National Handwashing Awareness Week (Dec. 1–7) (Only US)
- **International Day of Disabled Persons (Dec. 3)**

International Day of Disabled Persons (Dec. 3 2019)
2019 Theme: Promoting the participation of persons with disabilities and their leadership: taking action on the 2030 Development Agenda.

The annual International Day of Disabled Persons was proclaimed in 1992 by United Nations General Assembly resolution 47/3. It aims to promote the rights and well-being of persons with disabilities in all spheres of society and development, and to increase awareness of the situation of persons with disabilities in every aspect of political, social, economic and cultural life. Last year, the International Day of Persons with Disabilities (IDPD) focused on the empowerment of persons with disabilities for inclusive, equitable and sustainable development as anticipated in the 2030 Agenda for Sustainable Development, which pledges to 'leave no one behind' and recognizes disability as a cross-cutting issue, to be considered in the implementation of its 17 Sustainable Development Goals (SDGs).

January 2020

- World Braille Day (Jan. 4)
- **Moebius Syndrome Day (Jan. 24)**
- World Leprosy Day (Jan. 31) (was done last issue)



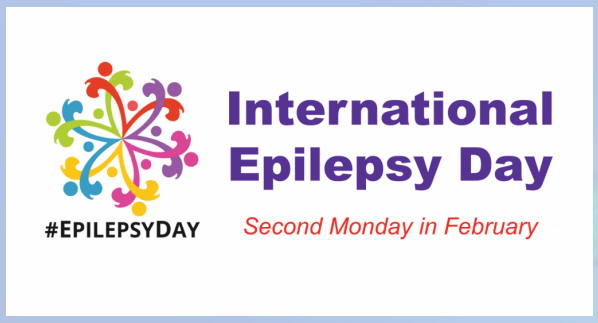
Moebius Syndrome Day (Jan. 24 2020)

The Moebius Syndrome Awareness Day is an annual event celebrated globally each year on January 24th — the birth date of Professor Paul Julius Moebius, the doctor who first diagnosed the condition in 1888. The goal of Moebius Syndrome Awareness Day is to raise awareness about the rare condition and to educate the world. Each year participants are encouraged to wear purple and raise awareness through various means and channels.[45]

Moebius Syndrome is a syndrome that is characterised by the presence of both congenital non-progressive facial weakness and the inability to move one or both eyes away from the nose (also called abducting the eye). Patients have difficulty or an inability to form facial expressions, which has many implications in social life. Besides these, those affected may also present a host of other symptoms including but not limited to misalignment of the eyes, hearing loss, congenital heart disease and autism.[46]

February 2020

- **International Epilepsy Day (Feb. 10)**



International Epilepsy Day (Feb. 10 2020)

International Epilepsy Day is a special event which promotes awareness of epilepsy in more than 120 countries each year. Annually, on the second Monday of February people join together to celebrate and highlight the problems faced by people with epilepsy, their families and carers.[47]

The brain runs on electrical signalling between neurons, so electrical activity is always present in the brain. A seizure happens when there is a sudden burst of intense electrical activity in the brain, also called epileptic activity. The epileptic activity causes a disruption in the normal electrical signals of the brain, so the brain's messages become mixed up. As the brain is responsible for all the functions of your body, this can have severe results. The specific effects of a seizure will depend on where in the brain the epileptic activity begins, and how widely and quickly it spreads. For this reason, there are many different types of seizures, and each patient experiences epilepsy in a way that is unique to them.[48]

March 2020

- World Hearing Day (Mar. 3)
- **World Kidney Day (Mar. 12)**
- International Day of Sleep (Mar. 13)

World Kidney Day (Mar. 12 2020)

Kidney disease currently affects around 850 million people worldwide. One in ten adults has chronic kidney disease (CKD), and the global burden of CKD is increasing. It is projected to become the 5th most common cause of years of life lost globally by 2040. Chronic kidney disease is a major cause of catastrophic health expenditure. In low-income and middle-income countries, most people with kidney failure have insufficient access to lifesaving dialysis and kidney transplantation.

Crucially, kidney disease can be prevented and progression to end-stage kidney disease can be delayed with appropriate access to basic diagnostics and early treatment. However, while national policies and strategies for NCDs in general are present in many countries, specific policies directed toward education and awareness about kidney disease as well as CKD screening, management and treatment are often lacking. There is a need to increase the awareness of the importance of preventive measures throughout populations, professionals and policy makers.

This year World Kidney Day continues to raise awareness of the increasing burden of kidney diseases worldwide and to strive for kidney health for everyone, everywhere. Specifically, the 2020 campaign highlights the importance of preventive interventions to avert the onset and progression of kidney disease. [49]

April 2020

- World Autism Awareness Day (Ap. 2)
- **World Hemophilia Day (Ap. 17)**
- World Malaria Day (Ap. 25)

World Hemophilia Day (Ap. 17 2020)

April 17, 2020 is the 30th anniversary of World Hemophilia Day! The theme of World Hemophilia Day in 2020 is "Get+involved". It's a call to action for everyone to help drive the WFH vision of "Treatment for all" at the community and global level.[50]

Hemophilia is a bleeding disorder that affects approximately 1 in 10,000 people. People with hemophilia do not have enough clotting factor VIII or IX in their blood. As a result, they can bleed for longer than normal. The most common bleeding disorder is von Willebrand disease (VWD). It is generally less severe than other bleeding disorders. Many people with VWD may not know that they have the disorder because their bleeding symptoms are very mild. Rare clotting factor deficiencies are disorders in which one of several clotting factors is missing or not working properly. Less is known about these disorders because they are diagnosed so rarely. In fact, many have only been discovered in the last 40 years. Finally, inherited platelet disorders are conditions in which platelets don't work the way they should, resulting in a tendency to bleed or bruise.[51]

History of Vaccination

Infectious diseases such as smallpox, diphtheria, measles and pertussis killed many children around the world in the past. The introduction of vaccines has greatly reduced deaths resulting from such diseases. Many aspects regarding vaccines have changed in the course of time: several of these will be discussed below.

The First Vaccine

The first vaccination was performed by Edward Jenner in 1796. He was the local practitioner and surgeon in his hometown Berkeley in England, where he was born in 1749 and grew up during the Enlightenment. In order to conduct one of the first clinical trials, he combined the observation that milkmaids who had been infected with cowpox were immune to outbreaks of smallpoxs, with the scientific methods of observation and experimentation. After Jenner took pus from a cowpox lesion of an infected milkmaid, he rubbed it into scratches in the skin of James Phipps, the son of his gardener. The boy became a little ill afterwards. This showed that cowpox could pass from person to person. Next, he variolated the boy with smallpox and James was unaffected, also in the future. Jenner repeated this experiment 12 more times. By this, he provided an alternative to variolation, which had been practised in Asia since the 17th century. [52]. Variolation is the method of immunisation where a live virus is administered and is usually used to refer to the smallpox variolation (Variola means smallpox virus). Vaccination, on the other hand, is an immunisation method where attenuated viruses are administered. [53]

Jenner's statement that cowpox protects humans from smallpox infections is the base of modern vaccinology.
Until 1885, the term vaccine was only used for cowpox inoculation for smallpox. Louis Pasteur changed this when he developed a rabies vaccine (which later turned out to be an antitoxin). From then on, the term included all inoculating agents [54].

Status of Vaccines

As a result of Jenner's discoveries, vaccination was included in the many national health programs. Rulers of countries set up huge vaccination campaigns to show their positive attitude towards science and the health of their citizens. Even though vaccines were seen as a sign of national pride and prestige in the beginning, people considered vaccines necessary soon thereafter. In the 19th century, smallpox vaccination was made compulsory in Europe and North America. More vaccines were produced in the 20th century and vaccination of children became a requirement for public school attendance.

Vaccine programs went global after the WHO and UNICEF were founded in 1948 and 1946, respectively. An example of a successful campaign performed by the WHO was the smallpox campaign in the 1960s and 1970s, which resulted in the last naturally occurring case of smallpox in 1977 [54].

Safety of Vaccines

In Jenner's lifetime, none of the quality control and sterilisation methods we know nowadays were present. In the beginning of vaccination, lymph from pustules on the arms was extracted in order to be used on another person. With this method, other microorganisms could easily be transferred, which lead to the spreading of diseases.

Over time, quality control, sterilisation, monitoring and supervision so that vaccines do not cause serious infections have become an important part of vaccination. An example of a time when this went wrong was in 1955: 200 children became ill, of which 5 died, after receiving a vaccine containing active wild-type polio virus [54].

Different Types of Vaccines

Since this first vaccine, different techniques have been developed and improved to produce vaccines. These include attenuation, inactivation, purified proteins, polysaccharides, conjugation and genetic engineering.

18/19th Century

The first technology to be used was attenuation, when Edward Jenner used it to create the smallpox vaccine. However, it was Louis Pasteur who elaborated on the concept of attenuation. He proved this with Pasteurella multocida in chickens, Bacillus anthracis in sheep, and the rabies virus in animals and humans, which he is most famous for (together with his pasteurisation technique). Approaches such as exposure to heat and oxygen were used. About 40 years later, a vaccine for tuberculosis was created, and this time a more powerful technique for attenuation was used: Mycobacterium bovis was cultivated 230 times in an artificial medium. This attenuated the infectious agents more compared to the methods used before.

At the end of the 19th century, the first inactivated vaccine was developed, based upon the discovery that bacteria keep their immunogenicity when killed by heat or chemicals. With this method, vaccines were developed for typhoid, cholera and the plague at the end of the 19th century. [55]

First Half 20th Century

In the first half of the 20th century, a revolution in the world of vaccination took place when it was discovered that in vitro cultured cells could be used as substrates for viral growth. Many viruses could be grown in cell culture, including polio and measles. Using this method, the viruses with the best ability to grow in the medium survived, which often had mutations that lead to the loss of the ability to infect and spread. Many vaccines, including those for polio, rubella, mumps and varicella, were developed this way. [55]

A development in the inactivated vaccines also took place around that time. Research of Kendrick and Eldering on a pertussis (whooping cough) vaccine lead to standardisation of whole-cell vaccines.

The influenza vaccine was the first successful inactivated virus vaccine. Later in the 20th century, more inactivated virus vaccines were developed, like polio and hepatitis A vaccines that were produced using chemical inactivation.

End of the 20th Century

Another type of vaccine was developed after the discovery that many pathogens are covered by a polysaccharide capsule. The first vaccine based on this was the meningococcal polysaccharide vaccine, that consists of capsular polysaccharides [56]. The idea is that antibodies against the capsule stimulate phagocytosis. Not much later, a combination of pneumococcal polysaccharides was produced to prevent invasive infections and this concept was also used for a Hemophilus influenza type B vaccine.

The polysaccharides were often coupled to a conjugate protein, because the polysaccharide alone was not able to start a B-cell response in infants. In the early 21th century, this principle was applied to meningococcal and pneumococcal vaccines which resulted in a better control of infections and spreading.

There were also vaccines that are protein based. Diphtheria and tetanus toxoids were already used in the beginning of the 20th century. This method was also used to improve some other vaccines, like the whole-cell pertussis vaccine, that was mostly replaced by acellular vaccines in order to reduce unwanted reactions.

Another technique called reassortment was used to create a new kind of attenuated vaccines. Three major vaccines, one live influenza vaccine, one inactivated influenza vaccine, and one rotavirus vaccine, were developed using this technique [55]. Reassortment is also a natural process: viruses swap gene segments, which they are able to do because certain viruses have a segmented genome. When two viruses co-infect a cell, new viruses with segments of both viruses emerge. This leads to viral diversity [57]. During the development of vaccines, viruses that were still immunogenic but were safe to handle were created by selecting the wanted segments and combining them [55].

Near the end of the 20th century, genetic engineering started to be used in vaccine development. By placing the coding sequence for certain antigens in yeast, animal or insect cells, large amounts of antigens could be produced.

Research into many viruses and bacteria was done to determine if they could be used as vectors for the production of antigens. An example of a vaccine created in this way is the Hepatitis B surface antigen recombinant vaccine [55].

The HPV vaccine is based on the L1 protein the virus contains. This protein induces protective antibodies, but more importantly, it aggregates to form immunogenic VLPs (virus-like particles).

Reverse vaccinology is the process of antigen discovery starting from genome information. This technique was first used for a meningococcal group B vaccine licensed in 2013 and is now seen as a successful method of vaccine discovery [58].

Protesting against Vaccination

Nowadays, when discussing vaccinations, anti-vaxxers come to mind immediately. But protesting against vaccines did not emerge just recently. Back in the beginning of the 19th century, anti-vaccination movements existed already. The members claimed that their privacy and bodily integrity were intruded. Even though fear of vaccination in that time was probably based upon made up horror stories, there was some truth in their fear: the risk of infections induced by vaccines back then would not be acceptable now. [54]

Discussions if unvaccinated children are allowed in kindergarten and if vaccination leads to developmental disorders in children indicate that anti-vaccination is still a very actual topic.

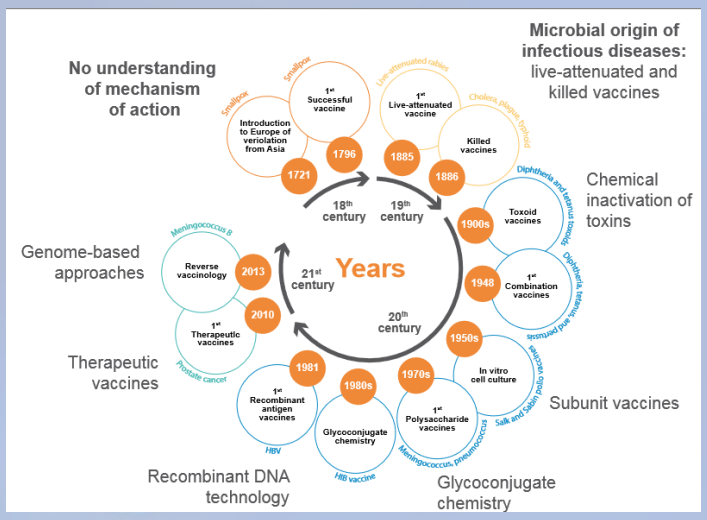


Figure 4: History of vaccine development [59]

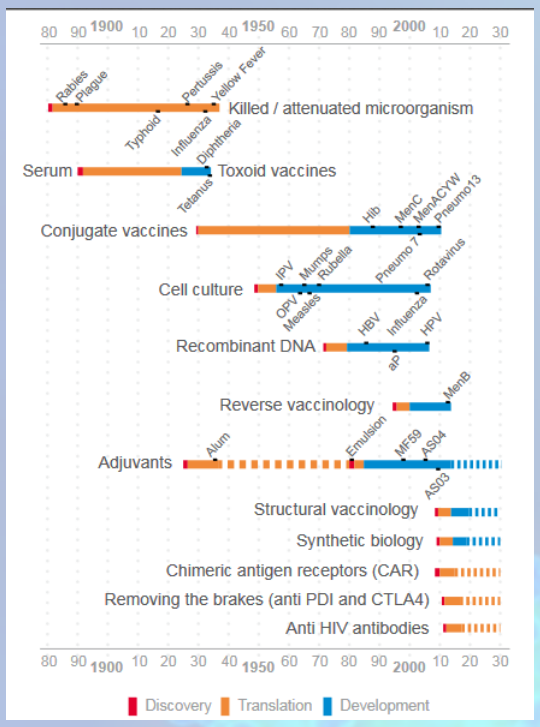


Figure 5: Discovery, translation, and development for various vaccines by technology [59]

Anti-Vaxxers

Despite the enormous benefits that vaccines have demonstrated over the last decades, misinformation and confusion are often spread via social media platforms. This has given rise to a movement that threatens the general public health of our world; anti-vaxxers. Anti-vaxxers are people, mainly parents, who doubt the safety, and sometimes even the use of vaccines. The resulting decrease in parents willing to vaccinate their children leads to outbreaks of diseases previously nearly eradicated, like the measles [60, 63].

The huge increase in discussion about vaccines and safety was first started by an article published by Andrew Wakefield et al. in 1998 in the Lancet [61]. The article was focussed on the measles, mumps, and rubella (MMR) vaccine, and concluded that vaccinated children might develop behavioural regression and developmental disorder, or in other words, autism [61]. Even though the study was quite flawed (small sample size, uncontrolled design, speculative conclusions), it received wide publicity, leading to a drop in MMR vaccination rates [62]. Shortly after Wakefield's article, epidemiological studies were published opposing his findings and showing no link between MMR vaccination and autism. Additionally, a conflict of interest was revealed, as Wakefield had been funded by lawyers who were working on lawsuits against vaccine-producing companies. Most important was the revelation that Wakefield et al. performed deliberate data fraud, by selectively choosing data and falsifying facts. In 2010, the article was completely retracted by the Lancet. However, the damage was already done, as the initial fear of vaccines causing autism developed into an anti-vaccine mind-set [62].

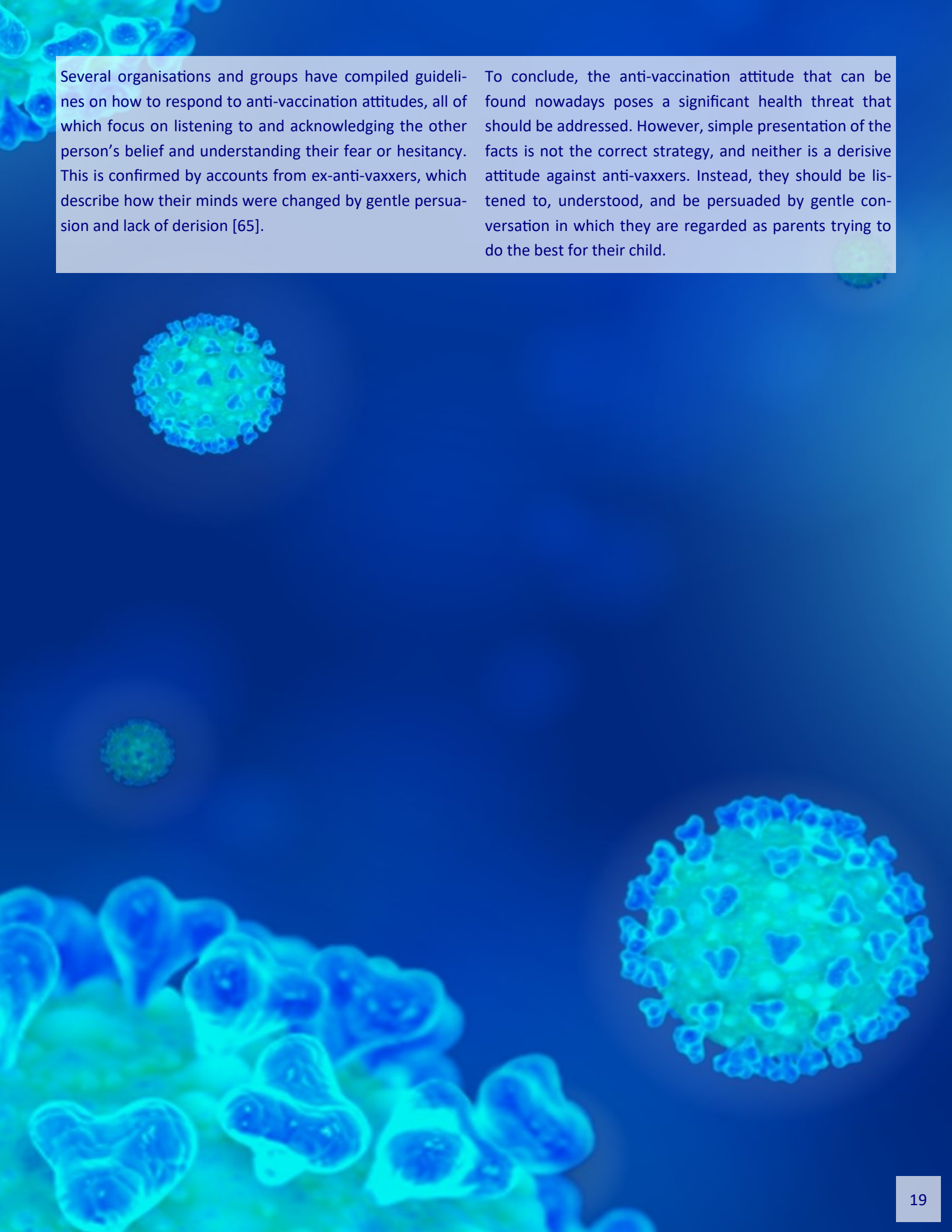
The possibility of online exchange of information amplified the fear and confusion around vaccines, allowing for the sharing of misinformation. Currently, a high percentage of the population searches for medical information on the internet [60], where they are willing to accept unreliable sources of information. A study in a group of students showed that 59% of participants who searched for information on vaccine dangers online perceived all information found to be correct, while at least half was incorrect [64]. Additionally, 53% showed misperceptions about vaccines after the search [64]. The main platforms via which anti-vaccine or incorrect information is shared are facebook groups, founded by anti-vaxxers. In these groups, information contrary to information given by health experts is shared, as well as information shared on the risks of vaccines, while leaving out all information about their benefits [60].

Many strategies have been attempted to change the hesitancy about vaccination and the anti-vaccine mindset. However, it has been shown that exposure to correct information about vaccines did not have a significant positive effect. People with an anti-vaxxers attitude reject information that discredits their beliefs even if scientifically proven, while they search for and accept information that confirms their beliefs [60]. Additionally, pro-vaccine campaigns can actually have an opposite effect, which is also seen in anti-tobacco, anti-alcohol and anti-marijuana campaigns [60]. The main reason that a presentation of facts is unable to convince anti-vaxxers is the involvement of emotional, cultural, political, and social factors [65]. Several strategies that have been shown to work, focus on mainly social and emotional factors.

Firstly, it is important to understand the anti-vaccination mind-set. Most people are not simply pro- or anti-vaccination, but part of a spectrum, in which the noisy group who declines all vaccination is the smallest. The group most likely to be convinced consist of hesitant parents who can be reassured. Secondly, information should be focussed not on the benefits of vaccination, but on the risks of refusing vaccinations. Thirdly, emotion is a very powerful motivator that is more engaged by personal stories. Human empathy decreases as the group of victims increases. Therefore, examples should be focussed on individuals. Lastly, and most importantly, courtesy is vital in changing the mind-set of anti-vaccine attitudes.

Several organisations and groups have compiled guidelines on how to respond to anti-vaccination attitudes, all of which focus on listening to and acknowledging the other person's belief and understanding their fear or hesitancy. This is confirmed by accounts from ex-anti-vaxxers, which describe how their minds were changed by gentle persuasion and lack of derision [65].

To conclude, the anti-vaccination attitude that can be found nowadays poses a significant health threat that should be addressed. However, simple presentation of the facts is not the correct strategy, and neither is a derisive attitude against anti-vaxxers. Instead, they should be listened to, understood, and be persuaded by gentle conversation in which they are regarded as parents trying to do the best for their child.



Antivirals

Previously, the mechanism and importance of vaccines for the prevention of viral infection was discussed. However, these vaccines have no to very little effect once an infection has begun. Antiviral medication is used to stop an infection once it has started. Unlike other classes of medication, antivirals do not destroy the pathogen but aim to stop its replication. Antivirals are mainly focused on viruses with prolonged and recurrent infections, since other infections will be dealt with by the immune system before a diagnosis is made.

History of Antivirals

The first mention of a specific therapy targeting a virus infection was in Rooyen and Rhodus' "Virus diseases of men" in 1946. In the beginning, it focused on the use of known antibiotics on virus infections. Following the empirical realization that this did not work, it was believed that selective toxicity for virus infection was impossible. There is some discussion about what the first antiviral therapy was. Some experts view the description of interferon in 1957 as the dawn of antiviral medication, whereas others see the description of idoxuridine (IDU) in 1959 as the dawn. In 1963, idoxuridine got FDA approval. In 2004, 46 years after the discovery of the first antiviral drug, 37 antiviral drugs were approved by the American FDA. In 2016, this number has more than doubled to more than 90, see figure 6. Showing that treatment of something that was once thought to be impossible, was now possible. [66]

Difficulties

Antiviral drugs are difficult to develop and approve, because the viral life cycle depends on host function. Affecting the virus without affecting the host cell is very difficult. This makes a lot of antiviral drugs fail somewhere in the development process, because of the side effects caused by cytotoxicity. For some early antiviral drugs only topical application was possible. Another difficulty lies in designing trials for antivirals, as many viruses do not have proper animal models which are needed for the approval of drugs. Only smallpox has gotten an exception to this rule by the American FDA because of its biological warfare threat. Furthermore, to be successful a drug targeting viral infection should inhibit hundred percent of pathogen activity. If not, the virus infection will restore to full extent with the risk of resistance being even bigger. [66, 67, 68]
There are 3 phases in the life cycle of a virus in which antiviral drugs can interfere. Figure 2 shows the subclasses within these 3 phases.

Before Cell Entry

The focus with this strategy is to prevent the virus from infiltrating the cells. To infiltrate a host cell the virus first has to enter the host. This can happen through, for example, an animal bite or sting, or through inhalation of the virus particles. The virus interacts with host cell receptors to penetrate the cell. Human immunodeficiency virus (HIV) binds to cell-surface receptors after which the virus fuses with the membrane of the host cell and injects the viral nucleic acid into the cytosol.

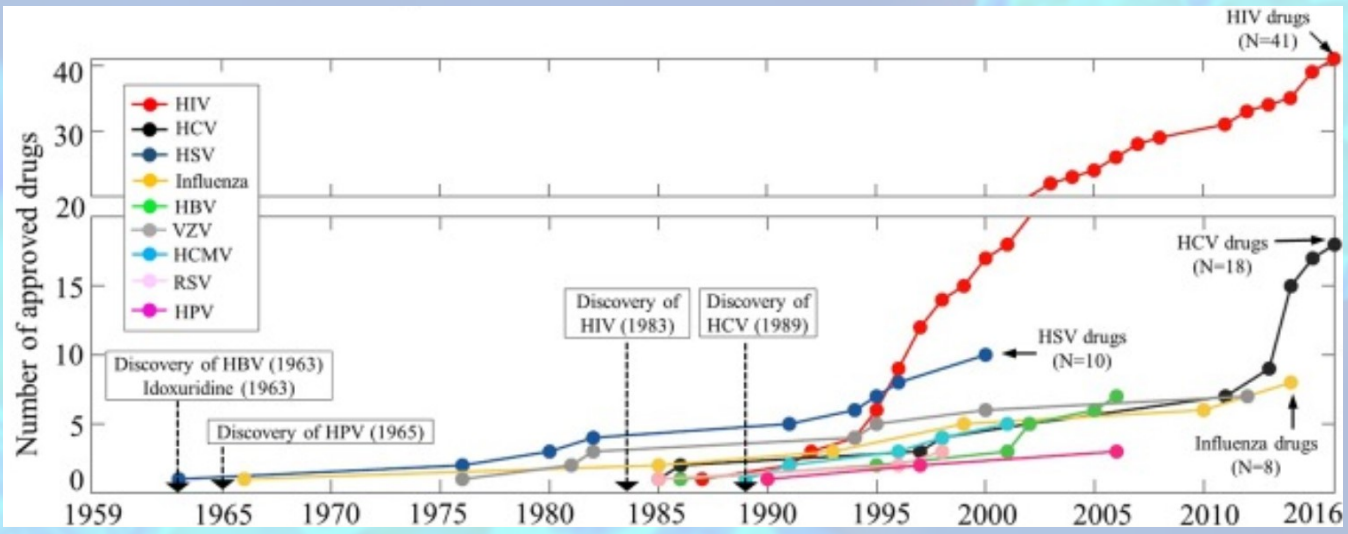


Figure 6: Number of approved antiviral drugs. [67]

Whilst the influenza virus enters the cell through receptor -mediated endocytosis after which the virus binds to coated pits and allows for endosomal membrane fusion. Both these pathways end with the viral nucleic acid being released in the cytosol where it replicates.

In some viruses the genome of the virus is released completely. This is called uncoating. Current strategies targeting viruses before cell infection focus on penetration and uncoating.[68]

Penetration

Viral entry is one of the most attractive targets for new antiviral therapies because of the absence of cellular access as a factor for drug activity. The entry process consists of three steps where interference is possible: (1) the virus attaching to the host cell, (2) co-receptor binding and (3) fusing of the virus with the membranes. In HIV when gp120-CD4 binding and co-receptor binding occurs, gp41 undergoes a transition into pre-hairpin intermediate structure. This structure exposes peptide motifs HR1 and HR2 which are essential for the formation of the six-helix bundle structure essential for fusion. Enfuvirtide binds to the HR1 region of gp41 blocking the formation of the essential hairpin structure, keeping the virus from fusing. [68]

Uncoating

Uncoating of the capsid happens at a low pH inside the endosomes. This is necessary for releasing the viral nucleic acid into the cytosol. In the Influenza virus A one of the main membrane proteins are the M2 channels. The M2 channel is a proton selective channel activated at low pH and it acidifies the interior of the virus which is essential for viral matrix protein dissociation. Amantadine blocks these M2 channels thereby inhibiting the uncoating of influenza A. [68]

During Virus Replication

The virus life cycle consists of many steps. A lot of approaches regarding treating virus infections are focused on inhibiting steps in the virus synthesis process.

Viral Gene Expression

The next class of antivirals inhibit viral gene expression by inhibiting the cleavage of the polypeptide derived from the viral genome needed for individual non-structural proteins essential in the virus' life cycle. After the virus has directed the host cell to transcribe the uncoated RNA, or in other cases the newly synthesized mRNA, these mRNA strands are transcribed to form the viral proteins.[69] In the treatment of Hepatitis C, Telaprevir is a peptidomimetic inhibitor that inhibits the viral NS3/4A protease. This protease makes the expression of functional proteins possible by cleaving the polyprotein translated from the viral RNA.[70]

Polymerase Inhibitor

These drugs interfere with DNA polymerase, RNA polymerase and reverse transcriptase to inhibit viral genome replication. There are 5 main ways antivirals influence these processes. The first is indirect inhibition of DNA polymerase. An example is Valacyclovir, which inhibits viral DNA polymerase after being phosphorylated by viral kinases. It does this by incorporating into and terminating growing viral DNA chains and inactivating the viral DNA polymerase. The second is directly inhibiting DNA polymerase, like Foscarnet by mimicking the pyrophosphate product of the DNA polymerization reaction. Thirdly, this can be done by directly inhibiting the RNA polymerase like Dasabuvir or indirectly by drugs such as Sofosbuvir . Lastly, efavirenz disrupts the joining of deoxyribose nucleotides with the template strand by binding near the catalytic site of the reverse transcriptase.[69]

NS5A Inhibitor

NS5A is a protein found in the viral RNA of the Hepatitis C virus. It plays an important role in genome replication and has been hypothesized to also affect apoptosis. Drugs like Ombitasvir inhibit this protein causing inhibition of viral genome replication.

Viral Integration

In HIV, HIV-1 integrase catalysis two reactions that insert viral DNA into that of the host cell. Drugs such as Raltegravir inhibit this enzyme, thereby inhibiting the replication of HIV.[69]

Viral Maturation

For viral maturation of HIV, HIV protease is needed. Drugs such as saquinavir bind to the active site of proteases, inhibiting their ability to cleave and mature the polyprotein. This leads to release of only immature HIV virions from the cell. These are non-infectious causing the virus to be unable to replicate.

Viral Release

After the virus has undergone the replication, translation and synthetization processes, the newly formed virions leave the cell to infect other cells. This is the last phase in which the infection can be interfered with as well.

Neuraminidase proteins allow the influenza virus to be released from the host cell and infect other cells. Neuraminidase inhibitors such as Zanamivir inhibit this protein binding to the active site. This causes the virus to be locked inside the cell and not infect other cells, which causes the virus infection to die out.

Resistance

Drug resistance is becoming a big problem for drug development. Treatment of a lot of diseases that used to be treatable are now made more difficult by drug resistance. This is because of the fast mutation rate of viruses and the relatively slow development of new drugs. In extreme cases, like in some areas of China, multi drug resistance occurs in up to 99% of the Gonorrhoeae isolates. Viruses are no different, as they replicate efficiently and mutate quickly. Any antiviral that will ever be made will have a virus resistant to it because of the fast mutation and because of the large number of viruses. When a virus becomes resistant to a drug, the treatment no longer works. A solution for this is to change medication, however only for HIV there is ample choice in drugs. Resistance can be avoided or delayed by combining drugs in treatment and new research is being performed towards finding a way around resistance and the development of drugs with a lower risk of resistance. [68, 69]

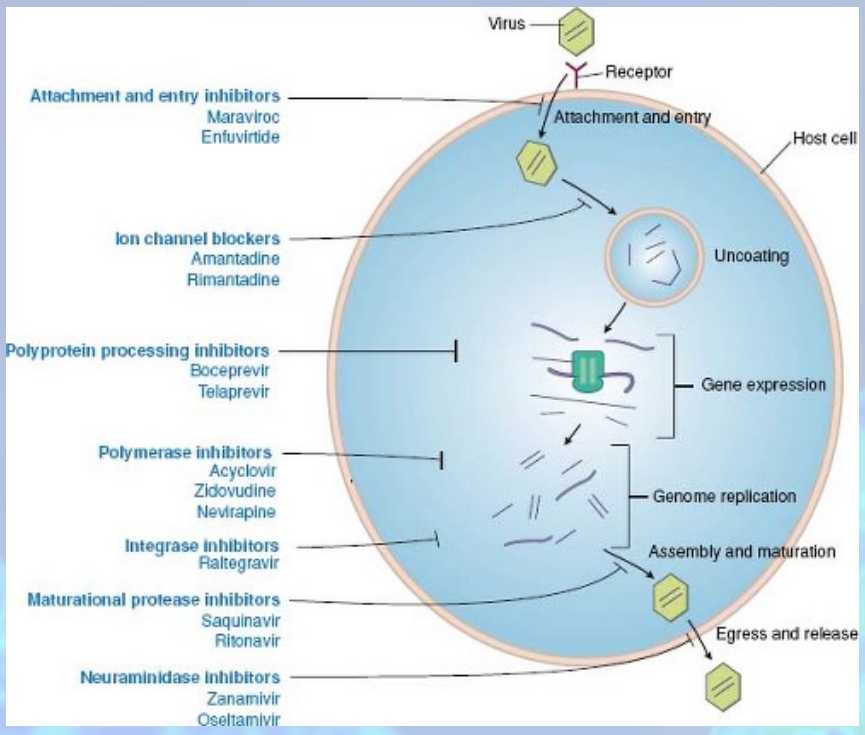


Figure 7: overview of classes and examples of antivirals [69]

Vaccines in Development

Vaccines are available for 26 diseases already, according to the WHO [71], but the research on this topic is not standing still: there are many clinical trials going on.

The World Health Organization keeps track of available vaccines and vaccines in development. These new vaccines are included in the Vaccine Pipeline. The newest version of the pipeline exists of seven pathogen areas: HIV, malaria, tuberculosis, Respiratory Syncytial Virus (RSV), Enterotoxigenic E. Coli (ETEC), Shigella and Norovirus [72]. HIV, malaria, tuberculosis and RSV will be discussed in this article, as these diseases cause millions of deaths a year globally.

HIV

At the moment, there is no HIV vaccine available. However, in the last couple of years, a lot of trials concerning the safety and dose of different types of vaccines in both animals and humans have been started or completed. Types of vaccines include those based on monoclonal antibodies and DNA. Most of these are in phase 1 trials and a few have already progressed to phase 2 trials [73].
An example of an ongoing HIV trial is the randomized, double-blind placebo-controlled trial where eight different vaccine regimes are tested for their safety and tolerability in healthy humans [74]. After a screening period of 4 weeks, participants received a vaccine at week 0, 12, 24 and 48. The study vaccines are Ad26.Mos.HIV, MVA-Mosaic, gp140 DP (and placebo). These vaccines elicit polyfunctional antibody responses [75]. Ad26.Mos.HIV is an abbreviation for adenovirus serotype 26-Mosaic -Human Immunodeficiency Virus. It is a mosaic vaccine, which means pieces of a variety of HIV strains are combined [76]. MVA-mosaic stands for Modified Vaccinia Ankara Mosaic. Modified Vaccinia Ankara, a replication-deficient viral vector, is used to deliver a mosaic HIV-1 vaccine [77]. Gp140 DP is HIV type 1 Clade C glycoprotein 140 drug product [74].

All participants randomized to a non-placebo regime received Ad26.Mos.HIV in week 0 and 12. In week 24 and 48, the different groups received different vaccines or different doses. There is a follow up period of two years. Primary outcomes are adverse effects in all 96 weeks and local and systemic reactogenicity for 8 days after every vaccination.

There are also ongoing trials with other types of vaccines: vaccines that elicit V2-specific antibody responses, vaccines that elicit effector memory T-cells at mucosal sites of infection and vaccines that elicit or deliver broadly neutralizing antibodies [75].

Malaria

RTS,S (Mosquirix), approved in 2015, is the only malaria vaccine available at the moment. RTS,S is a recombinant protein against the circumsporozoite protein (CSP) of Plasmodium falciparum, the parasite that causes malaria [78]. This protein is expressed in the pre-erythrocytic stage, a metabolically active but asymptomatic stage of the life cycle of the parasite [79].

The effects of this vaccine were assessed in a large phase 3 trial and although the evaluation turned out positive, there are several unclarities that need to be resolved before it can be implemented for routine use [80]. In a pilot in three African countries, the following issues will be addressed:

- The possibility to provide the malaria vaccine at the recommended 4-dose schedule, due to health service delivery in these countries.
- The influence of the vaccine, in combination with other interventions, on child mortality, separated by sex. Other interventions include insecticide-treated bed nets, indoor spraying with insecticides and access to malaria testing and treatment [81].
- Adverse effects such as meningitis and cerebral malaria, also separated by sex.
- Systematic collection of evidence on immunization programme, adherence to malaria control measures, and also on broader health system functioning and community engagement.

The pilot, which started in 2019, takes place in Ghana, Kenya and Malawi. These countries are chosen based on the presence of well-functioning malaria and immunization programmes and areas with moderate to high malaria transmission. For this pilot, 10 million vaccine doses were donated [81].

However, in the last couple of years, multiple clinical trials with other vaccines than RTS,S were conducted or are still going on. These include PfSPZ, an inactivated whole organism, and ChAd63/MVA ME-TRAP, a recombinant viral vector [73].

Tuberculosis

Right now, there is a vaccine available for tuberculosis, named Bacille Calmette-Guérin (BCG). This vaccine protects against severe extrapulmonary forms of tuberculosis, but has no reliable protective properties against pulmonary tuberculosis, which has a higher disease burden [82]. Therefore, it is important research into a new vaccine continues. There are multiple candidates, including Ad5Ag85A and MVA85A, both recombinant viral vectors [73].

A trial that is currently taking place, called 'Phase 1, Open-label Clinical Trial to Evaluate the Safety and Immunogenicity of an Adenovirus-based Tuberculosis Vaccine Administered by Aerosol', evaluates the safety and immune responses after aerosol administration of Ad5Ag85A in healthy volunteers who have received the BCG vaccine before [83]. Ad5Ag85A consists of a recombinant, replication deficient, human adenovirus - Ad5 - containing the immunodominant antigen Ag85A. Primary outcomes are adverse events at 48-72 hours after vaccination, and over a period of 24 weeks afterwards. Recruitment is still open and the estimated completion date is in 2021.

RSV

After approximately 50 years of failed attempts to create a RSV vaccine, there is now a promising candidate, called DS-Cav1 or VRC 317 [84]. Protein F, a part of RSV, is known to induce an antibody response in humans. The problem is that there are two conformational states of this protein: pre-fusion and postfusion [85]. The immune system only reacts effectively to the pre-fusion conformation [84] and therefore, the vaccine needs to contain the pre-fusion protein. Mutations to stabilize the pre-fusion conformation and to prevent the rearrangement into the postfusion conformation were made in order to create DS -Cav1 [85].

A phase 1 trial with this vaccine started in 2017 and is estimated to finish in 2020. The safety and tolerability of intramuscular administration of Ds-Cav1 alone or with adjuvant is evaluated in healthy adults during 44 weeks [86]. An analysis of the results so far showed that the vaccine caused a more than 10-fold increase in neutralizing antibodies when compared to the amount of antibodies naturally produced after RSV exposure earlier in life [84].
There are few other possible vaccine candidates [73].

Meet the Expert: Frank van Kuppeveld

Prof. dr. Frank van Kuppeveld is the chair of the virology department here, at Utrecht University. With more than 200 publications and over 7000 citations, you can say he is accomplished in his field. He started his journey at the Radboud University in Nijmegen with a major in Molecular Biology and continued his research there for several years. Nowadays, he works at the Androculus building at the Faculty of Veterinary Medicine and focuses on developing new antiviral strategies He is especially interested in viral replication, the role of viral enzymes, and the impact of the virus on the host cell.. We interviewed him about his research, antiviral and vaccine development, and his opinions about the development of drugs against COVID-19.

His Research

He focuses predominantly on picornaviruses, small (pico) RNA viruses, which include rhinoviruses and enteroviruses. The latter is his main focal point, according to him purely out of scientific interest. One of the most well-known enteroviruses is the poliovirus. However, this group consists of many more. For example, the upcoming enterovirus D68. Since the days of the poliovirus, there have not been as many cases of paralysis as a consequence of infection as now with this D68-virus. The reason why this virus reaches the brain more easily than other enteroviruses is not yet known, but this is one of the questions he tries to answer.

Antiviral Therapy VS Vaccination

Using the collected information on the role of viral and host enzymes, he tries to identify targets for antiviral drugs. This type of drug requires detailed knowledge on the mechanisms behind the virus, and the role of the viral enzymes and host enzymes. Contrastingly, he explains that vaccine development can be as simple as inducing B-cells, antibodies, or sometimes T-cells. Most of the time all you need is to do is inject antibodies to gain protection against a virus. The first vaccines in the 60's and 70's were designed without real understanding of their mechanism of action. They either replicated the virus, added formaldehyde, and injected the inactivated virus or they passaged the virus so many times it lost its essential genes for immune suppression, and injected the attenuated virus. With antivirals, a more thought-out approach is needed. You need to be aware of the target of your molecule.

Answering the question when he would recommend antiviral therapy and when vaccination, he explained that they are complementary. Preferably, you want a vaccine to prevent transmission and infection. However, for the infected, prevention by vaccination will serve no purpose. When there is an outbreak, you will want to stop the virus early on using antiviral drugs to stop the infection as well as using vaccination to avoid transmission. Vaccination can also be virus specific, which makes it a time consuming approach as you will have to develop them one at a time. Antivirals would then be preferred as they can target a viral component shared by many types of viruses.

Antiviral Development

Antivirals target either components from the virus or components from the host. As viral enzymes are similar, but not identical, finding a broad-working antiviral can be more easily achieved by targeting host enzymes. To determine which enzymes are fundamental for viral replication, Van Kuppeveld uses genetic screening, such as CRISPR screens and siRNA screens. Even though almost every drug targets the host, this approach has its downsides. He emphasized the importance of concentration and duration, as an increase in both can increase the amount of side-effects. You need to find the right balance.

Most therapeutic antibodies target the proteins on the head of the virus as most neutralising epitopes are located there. However, this part of the virus is very susceptible to genetic variation and viral escape, which can result in antiviral resistance. Therefore, multiple therapies have been developed for most infections. For example, against HIV there are 3 or 4 molecules in case the virus becomes resistant to one. To combat this problem, a novel method is being developed that targets not the head, but the stem of the virus. He describes this method as the holy grail in antiviral research as the stem is highly conserved.

Additionally, barely any antibodies are being produced against this part during an infection as the head is immunodominant. He further explains that therapeutic antibodies directed at the stem are therefore not prone to viral resistance and if the stem does mutate it is likely to have a large negative impact on its overall fitness.

Drug Specificity

Recently, Van Kuppeveld tested various FDA-approved drugs on enteroviruses. As a result, itraconazole, a drug against fungi infections, showed promise as a viral inhibitor. A more surprising discovery Van Kuppeveld made during these tests is that fluoxetine, also known as Prozac, possesses antiviral properties. This antidepressant was developed to target the serotonin reuptake receptor, and it was not yet known that the molecule inhibits viral replication. After testing other antidepressants with similar mechanisms of action, none showed the same antiviral effect. To discover why fluoxetine acted as a viral inhibitor, he added the drug to the virus in such a small concentration that the virus was still able to replicate. He performed a serial passage during which there was a period of illness with a low replication rate followed by a period of viral growth. The cause of this growth was two point mutations in the helicase, a class of viral enzymes, which resulted in resistance against fluoxetine. This was an indication that the drug directly targets that enzyme. His team managed to make crystal structures that provided evidence that it indeed binds to a pocket of a helicase. He is currently working with a medicinal chemist to improve the structure-activity relationship that will increase the potency of the molecule as an antiviral.

This example illustrates the unpredictability of drugs. More often than not, they target more than one binding site, which can cause many side effects, or, as can be seen from this example, can lead to surprising and exciting alternative purposes.

COVID-19

As chair virologist, Frank van Kuppeveld is involved in the search for a vaccine and/or antiviral against COVID-19. At arrival in his office, the virus clearly was top priority. Many articles on COVID-19 were on his desk, he was still in an important meeting discussing research possibilities on Corona, and was leaving that week to a WHO convention in Geneva. This was February 7th. Then, not much was known about the development of a potential vaccine or antiviral against this highly infectious virus. We asked him about the possibilities of antiviral and vaccine development against the imminent spread of COVID-19 throughout Europe.

He stressed that the development as well as the production of vaccines were time-consuming. Especially the logistics behind the production are going to be problematic. He proposed a different method that lets the patient make their own vaccines. Several large firms, such as Moderna and Curevac, are currently developing messenger RNA vaccines for COVID-19. These types of vaccine consist of mRNA with an in vitro transcription of the coding information for the S-protein, which is present on the outside of the virus. After injection, the mRNA will be taken up by the body and the immune system will produce an antigen response. This novel type of vaccination should make the process quicker. Another possibility is the use of vector based vaccines or subunits. However, these require the production of a protein, which is more difficult to achieve.

Before the outbreak of this virus, Van Kuppeveld was working with other viruses from the Corona family, such as MERS and SARS. These viruses were more lethal during their outbreaks, but he explained that the COVID-19 outbreak is worse due to its high transmission rate. For example, the MERS-coronavirus never became a pandemic as it could only be spread from camel to human,

not human to human. Also contributing to the infectiousness are the patients with fewer symptoms that can more easily transmit the virus. He found it unbelievable that such a large country as China could be shut down due to a viral outbreak. They are currently working on making therapeutic antibodies against the MERS- and SARS-viruses. One of the antibodies directed against SARS, has been discovered to bind to COVID-19 as well as that it is targeting an epitope that is fully conserved in this new Coronavirus.

Moreover, they investigated the possible use of existing drugs, as was the case with fluoxetine for enteroviruses. A HIV-protease inhibitor appears to have a protective effect against COVID-19, as well as some other antiviral drugs. However, the specifics were still unknown and being investigated.

Thus, even though many ideas are floating around concerning a possible vaccine or antiviral against COVID-19, at that moment there was not yet one concrete plan. However, there are a few potential candidates he and his colleagues are trying to get developed quickly. Preferably, he would like to see the development of a drug with a broad-working activity targeting all corona-viruses to prevent another outbreak by this family. Sadly, funding does not allow for the extensive research needed to achieve this. Overall, COVID-19 antiviral drug and vaccine development was in the beginning of February still at an early stage and far from being produced and distributed to prevent the upcoming pandemic.

As the interview was conducted in Dutch, some of the context might be lost in translation.

Cancer Vaccination

As one of the earlier articles in this issue explained, vaccines against infectious diseases were first realised in the 18th century. This had a big impact on health and longevity across societies. Child mortality rates dropped, and some deadly diseases, like smallpox and rinderpest, have been completely eradicated, while others, like the measles and polio, have become extremely rare [87]. Since stimulating the body's own immune system to fight the disease was so effective for infectious diseases, it seems only logical this technique was extended to other diseases, like cancer. The first attempt to stimulate the immune system to fight the cancer was actually already done in 1891, by Dr. William Coley, who injected inactivated bacteria into cancer patients to induce a state of immune activation [88]. Even though the scientific community was sceptical, his 'vaccine' effectively decreased tumour growth, and nowadays vaccines are a large field of interest and research in oncology [89].

Two types of cancer vaccines exist, prophylactic vaccines and therapeutic vaccines [90]. Prophylactic vaccines are meant to prevent or delay the onset of cancer, which is mainly done for cancers that are caused by viruses. Currently, two prophylactic cancer vaccines have been approved. The first targets the hepatitis B virus (HBV), which is associated with development of hepatocellular carcinoma, and the second targets the human papillomavirus (HPV), which is associated with development of cervical cancer [90]. These vaccines prevent infection by the virus, which in turn prevents the development of the cancers associated with these viruses.

Therapeutic cancer vaccines are meant to target cancers that have already developed. In cancer, the tumour uses several tactics to protect it from being attacked by the immune system. One of the main tactics is to prevent the release of 'danger signals' that are normally released in the case of a disease [91]. Without those signals, dendritic cells (DCs) are not activated to capture tumour antigens and use them to start a tumour-specific immune response [91]. Therapeutic cancer vaccines aim to cause activation of tumour specific T-cells with the use of tumour specific antigens and immune-activating delivery platforms.

Although the mechanism of immune activation is comparable across all cancer vaccines, a large variation in antigen type and delivery platform exists. Choice of the antigen is the most important component in designing a cancer vaccine, and as such, it needs to adhere to several criteria [92]. Firstly, It should of course be expressed on all tumour cells, without being expressed on healthy cells. Secondly, the antigen needs to be required for cancer cell survival, so it can not be downregulated to escape attack, and lastly, the antigen needs to be immunogenic, which means it is able to induce an immune response [92]. The group of antigens that fit these criteria can then be divided into several categories (Fig. 1). Previously, all research was focussed on the group of tumour-associated antigens (TAAs), which are self-proteins that are overexpressed on cancer cells. However, as they are self-antigens, B-cells and T-cells with strong specificity have been eliminated by tolerance mechanisms, which leads to a diminished immune response [93]. This can partly be alleviated by adjuvants to increase the immune response, but efficacy often remains insufficient [92]. Additionally, TAAs are often also expressed in low levels on healthy cells, which could lead to toxic side-effects [92]. Since the development of next generation sequencing techniques, a different type of antigens called neoantigens has become an option [94]. A neoantigen is a mutated protein that can be recognised by lymphocytes, and that can both be private, and shared across patients. As these mutated proteins are only expressed on tumour cells, these vaccines are very specific. Vaccines based on neoantigens are currently being tested in clinical trials. Tumour cells of patients are sequenced, and antigens are selected based on their predicted affinity for MHC molecules. Generally, 10-20 mutations are chosen to be administered to the patient in vaccine form [94].Once chosen, these antigens need to be administered in a way that causes a robust immune response. Three main types of delivery platforms have been designed for this purpose. The first, molecular vaccines, is the simplest [92].

The chosen antigen(s) are simply injected into the patient in the form of peptides, RNA, or DNA. However, several factors limit the efficacy of these vaccines, like lack of co-stimulation (mainly peptides), low uptake (DNA and RNA), and fast degradation (RNA). The second type consists of viral vectors [92]. These viruses, modified to express the antigen(s), are able to infect antigen presenting cells (APCs), leading to enhanced presentation of the antigen and immune activation [95]. A disadvantage is the strong antiviral immune response that prevents repeated administration of the vaccine [92]. The last and most used platform is cellular vaccines. Several different cellular vaccines have been tested, with varying efficacy, but the most common are the dendritic cell (DC) vaccines. DCs are seen as the most proficient APCs, due to their ability to cross-present extracellular molecules on MHC-I to CD8 T-cells, which is vital for an antitumor immune response [96]. DCs have been employed as cancer vaccines in various ways. They can be simply activated with inflammatory mediators; stimulated with antigens in vivo with the use of DC targeting delivery methods such as liposomes and vectors; transfected with genetic vectors for antigens; or stimulated in situ by intratumorally injected immunomodulatory agents or antigens [96]. However, the most common method is ex-vivo stimulation of patient-derived DCs with antigens or tumour lysate, followed by maturation by a maturation cocktail [96].

Cancer vaccines alone have shown some very promising results, but even more so in combination with other anti-cancer drugs, like immune check-point inhibitors (CPIs) and adjuvants [92]. In particular the combination of cancer vaccines with CPIs might have synergistic effects, as CPIs deactivate the immune-suppressing properties of the tumour, while the vaccine activates the immune system [92]. The potential of such combinations was highlighted by a study in a mouse model of melanoma, in which a combination of a cancer vaccine, adjuvant and CPI lead to complete regression and long-term survival [97]. To conclude, cancer treatment is an alternative application of the vaccine strategy, with very promising results. Many different options in antigens and delivery platforms exist, so all vaccines can be optimised against cancer, and the first vaccines are already on the market. Even more promising are potential combinations of therapies to lead to a successful treatment of cancer. The development of cancer vaccines represents a large step forward for the concept of personalised medicine.

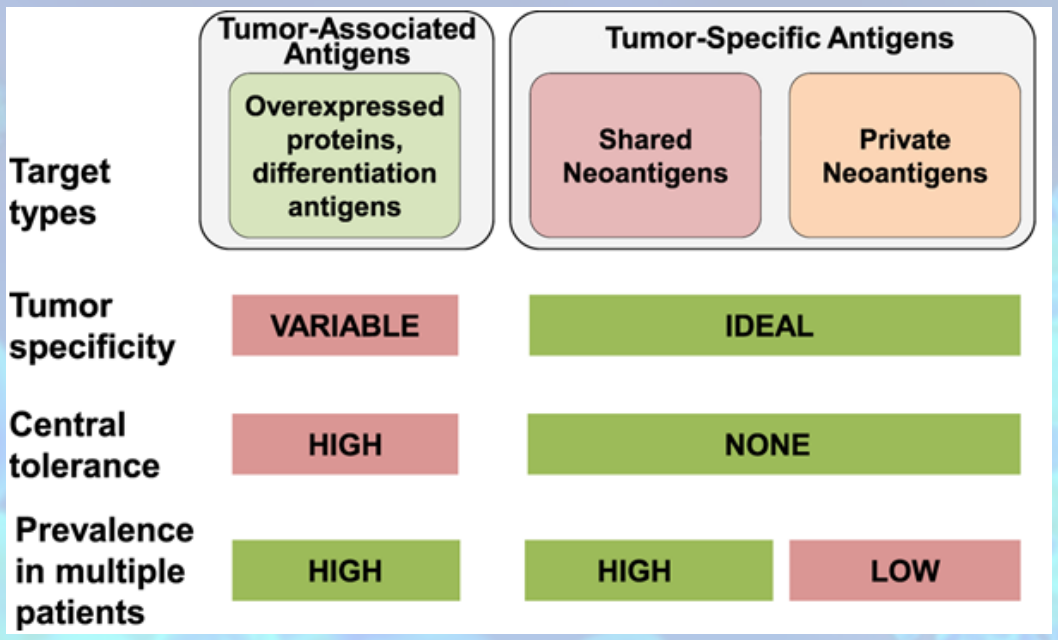


Figure 8: Possible types of antigens used for cancer vaccines and their characteristics.

Internship Joshua Elford

Transgalacto-oligosaccharides modulate DON immune toxicity in a murine dendritic cell model

Deoxynivalenol (DON), or commonly vomitoxin, presents a challenge due to its widespread prevalence in cereal products and resistance to removal from contaminated stocks. As a result, both humans and livestock are exposed to DON on an almost daily basis. Previously it has been demonstrated that upon exposure to the toxin, immune responses can be modulated towards a Th2 like response, with an increased likelihood of allergy development and a lesser response to pathogens. Considering exposure to DON occurs mainly in the human gut, a promising preventative measure could lie with human milk oligosaccharides (HMOS). These carbohydrate structures have been shown to modulate immune reactions in positive ways, by both influencing gut microbiome composition and by directly altering immune cell phenotypes. Transgalacto-oligosaccharide (TOS), which is just one of the large family of HMOS, may have promising immunomodulatory properties like those of galacto oligosaccharide or fructo oligosaccharide. The interaction between HMOS and immune cells occurs in the intestine, like that of DON, therefore they could have a restorative effect on the cell level disruption caused by the toxin.

In this study, the immune modulation of DON was evaluated in an in vitro murine DC model. Furthermore, the influence of TOS on immune cell disruption caused by the toxin was examined in terms of cell surface marker expression and cytokine secretion. The toxicity of DON was seen to differ from the previous studies on murine DCs, now showing cell death at 1 µM of DON. In addition, TOS significantly increased cell viability and affected other markers of immune activation, including modulating cytokine release in the presence of DON. This therefore positions TOS as another promising HMO and warrants further investigation into its potential as a dietary component.

Internship Patrycja Lenartowicz

Hacking the innate immune response through synthesis of the immunomodulator Lipid A

Multistep chemical synthesis of the key building block of Lipid A

Lipid A, the endotoxic principle of LPS present in the outer membrane of Gram-negative bacteria, initiates innate immune responses. Upon Lipid A binding, an m-shaped TLR-4-MD-2 dimer is formed. This dimerization is thought to occur by the acyl chain of the amine at the reducing end. Receptor dimerization leads to inflammatory cytokine production, which is a well-characterized feature of a beneficial innate immune response. However, overactivation of this proinflammatory signaling can result in the overproduction of cytokines and chemokines, which is thought to be the cause of septicemia. Yet, several studies have indicated that structural modification of Lipid A can lead to modulation of the innate immune response. Monophosphorylated Lipid A has already been used as an adjuvant, as it has been shown to induce the beneficial immune response without excessive production of proinflammatory cytokines. As the acyl chain of the amine at the reducing end appears to play a crucial role in receptor dimerization, it has been proposed that modifying the length of this acyl chain would modulate the innate immune response. In order to investigate this effect, a key building block towards the target Lipid A moiety was synthesized successfully. The synthetic route utilizes novel orthogonal protecting groups and requires fifteen steps. This building block will be used in further studies to synthesize derivatives of Lipid A in order to investigate their potential for use as immunomodulators for the treatment of septicemia and as adjuvants for vaccinations.

Latest News

David de Wied Building Getting EM Facility

The David de Wied building is one of the buildings at the Science Park in Utrecht, and currently thoroughly under construction in preparation for the arrival of new electron microscopes.

These new electron microscopes are high-end, very sensitive equipment and with this advancement, the university aims to create a research centre that will allow research in Life Sciences and Sustainability to get into the international top [98, 99]. For these microscopes, the DDW building will receive a new attachment, the EM-square. In figure 9 is a picture of the plans for the DDW. The entrance will be renewed and the EM-square will be attached to that. Since the microscopes are very sensitive to vibrations, a clever construction using the current foundations of the building will be made to prevent vibrations to be carried into the building and affect the microscope [100]. With the arrival of the microscopes, many researchers that are currently in the Kruyt building will be relocated to the DDW building to work with the microscopes. Some older electron microscopes from the Kruyt building will also be relocated to the EM-square. Since many new researchers will be housed in the building, the inside of the whole DDW building is also renovated, to be able to house these additional people. The renovation is expected to be finished at the end of 2020.[101]

Figure 9: Plans for the David de Wied building [100].

The new microscopes will allow a far higher resolution than the ones being used currently. Researchers will therefore be able to look at electrons surrounding atoms. This means they can see if an atom is charged and if it is in an excited state. This is valuable information for example for catalysts, since the state of the atoms is deciding for a material's catalytic properties. For cell biology this information can also be very valuable. [99]

Elsevier Journal 100% Open Access

As of 1 January 2020, researchers will be able to publish open access in all Elsevier Journals. The Association of Universities in the Netherlands (VSNU), The Netherlands Federation of University Medical Centres (NFU), The Dutch Research Council (NWO) and the information and analytics business Elsevier have come to this agreement in December 2019. It is in accordance with Plan S, which is a plan that started September 2018, for reaching full open access to all journals, and therefore make science overall more accessible. [102]

The agreement will be valid for January 1 2020 through May 1 2020. It means that, during this period, Dutch researchers will have full reading access to all Elsevier journals and are allowed unlimited open access publishing in all Elsevier journals. [102]

Molecular Insight in Alzheimer Disease

Scientists from the Utrecht University have done research into the understanding of Alzheimer disease on a molecular level. They have looked at the relation of aggregate formation to the behaviour of Tau protein, which is known to play a role in Alzheimer disease. They were especially interested in the way certain proteins bind to Tau proteins. It is known that Alzheimer disease is caused by the death of neurons caused by aggregation of the Tau protein in the brain. However, how exactly these aggregates kill neurons is not yet known, and therefore we cannot treat it very well. [103]

The researchers have made the first step in understanding this process and therefore in targeting the cause of the disease. They exposed Tau aggregates to a mixture of all the proteins present in the brain and used mass spectrometry to analyse their binding. They discovered that the proteins that bind to Tau aggregates all belong to classes that are known to play a role in the development of the disease. The mechanism with which they bind, called pi-stacking, is also very unusual and worth looking into, which is exactly what they did. [103]

They have looked further into the mechanism behind the protein aggregation and they published a paper on this in Nature Communications in January: “Arginine π-stacking drives binding to fibrils of the Alzheimer protein Tau.” In this paper, they show how arginine side-chains drive the protein binding in forming these Tau aggregates. Since it is not the charge that is important for this interaction, but the guanidinium group of these side-chains, pi-stacking has a key role. [103]

Important Discoveries in the Medical World

Kuru, the “Laughing Death”

In the history of diseases and discoveries, the mystery behind Kuru can be considered as the door to a whole new field of neurodegenerative disorders: the Transmissible Spongiform Encephalopathies (TSE). Being the first prion disease identified, Kuru has led several researchers to a Nobel prize: D. Carleton Gajdusek in 1976, Stanley B. Prusiner in 1997 and Kurt Wüthrich in 2002 [105].

Kuru is a fatal neurodegenerative disease characterised by an inflamed cerebellum, involuntary movements, tremors and emotional changes. Because of the emotional changes, patients experience inappropriate euphoria, depression, apprehension and compulsive laughter, hence the name “Laughing Death.” The clinical manifestations of Kuru can be divided into three stages: ambulant (patient can walk without support), sedentary (patient can sit without support) and terminal (patient is bedridden) [105,106]. On average, disease duration is 12 to 18 months before death occurs. From the 1940s to the 1960s, there was an epidemic of Kuru, restricted to the population of the Fore natives in the Okapa area of the highlands of Papua New Guinea. In total, Kuru has cost the lives of over 2700 people, approximately 7.5% of the entire Fore population.

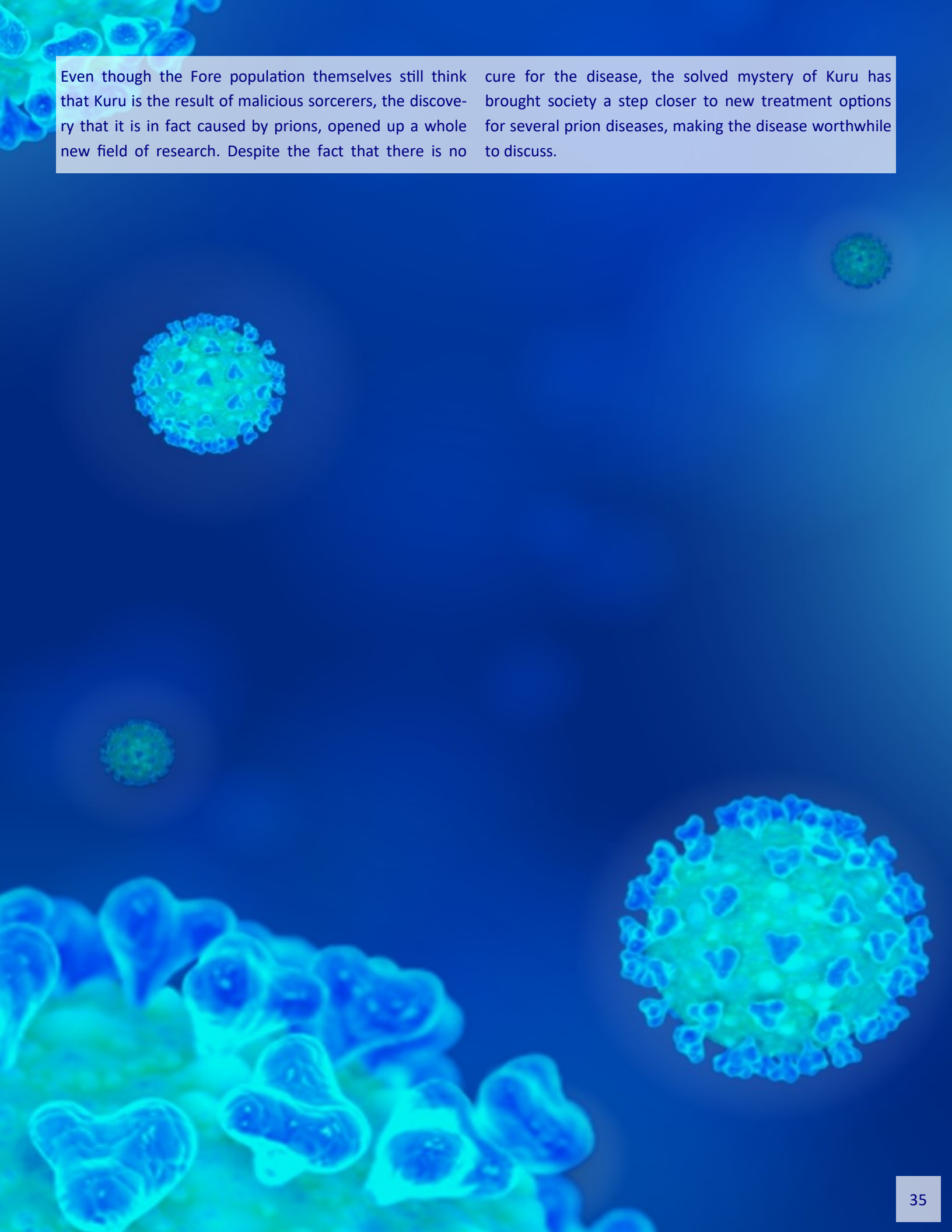
Upon first research it was thought that this disease was genetic, considering the facts that Kuru only occurred in Fore natives in the highlands of Papua New Guinea, and three quarters of the patients were related to someone who had already succumbed to Kuru. After it was discovered that the disease was transmissible to a variety of animals, this hypothesis changed: Kuru may be caused by an infectious agent that is spread through cannibalism, where genetics play a role in the susceptibility of a person to acquire Kuru [105].

Although this hypothesis was not completely wrong, it was not completely right either. Kuru is caused by the ingestion of prions [107]. Prions are misfolded proteins with the ability to misfold other, normal cellular proteins of the same structure. Prions will then form abnormal protein aggregates [107]. Researchers nowadays believe that prions are the sole cause of the disease. However, certain genetic mutations make a person more or less susceptible to Kuru, or cause either a short or long incubation time and duration. For example, a mutation in the gene for PRNP that codes for PrPc has a large influence on the susceptibility for or resistance against Kuru. If a person is homozygous for Met219, the disease will have a short incubation time. With the Met/Val and Val/Val 219 genetics, the incubation time is very long (up to more than 40 years), or the person may even survive entirely [105,107]. Because of the long incubation time (12 years on average), there are still very few cases of Kuru, even though no one has been exposed to the prions in a long time.

But how is one exposed to Kuru? The simple answer to this question is cannibalism. The people of the Fore tribes believed that by consuming the entire bodies of their passed relatives, the souls of the deceased reached the land of the dead, where they could be reborn as ancestors. As most of the body parts were eaten by women and children, they were more often exposed and thus more often victim of Kuru [105,107]. Because of the genetic susceptibility of Met/Met 219, there are now little to no Fore natives with this genetic variant, since they died before they could reproduce, resulting in natural selection [105].

Kuru has a lot of similarities with variant Creutzfeldt-Jakob -Disease (CJD). It was even because of Kuru that CJD could be identified as a prion disease. It is likely that the first case of Kuru, around the 1900s, was the result of the cannibalistic ritual of a deceased relative with sporadic CJD. People of a certain Fore tribe in the northwest of the territory then developed Kuru, and after they died, their bodies were eaten, thereby spreading the disease. Only after 1959, when the Australian government banned the cannibalistic practises, the incidence of Kuru decreased [105].

Even though the Fore population themselves still think that Kuru is the result of malicious sorcerers, the discovery that it is in fact caused by prions, opened up a whole new field of research. Despite the fact that there is no cure for the disease, the solved mystery of Kuru has brought society a step closer to new treatment options for several prion diseases, making the disease worthwhile to discuss.



References

Intro

1. Anti-Vaxxers When They Hit Their 4th Birthday My Time Has Come | Birthday Meme on ME.ME. (n.d.). Retrieved May 18, 2020, from https://me.me/i/anti-vaxxers-when-they-hit-their-4th-birthday-my-time-has-5c2cbe85ea15407caa4c43abf7424505
2. As Told by a Nurse — Antivaxxers be like…. (n.d.). Retrieved May 18, 2020, from https://astoldbyanurse.tumblr.com/post/162864748047/antivaxxers-be-like
3. People Can't Stop Trolling Anti-Vaxxers With Memes (30 Pics). (n.d.). Retrieved May 18, 2020, from https://www.boredpanda.com/funny-anti-vaxx-memes/?utm_source=google&utm_medium=organic&utm_campaign=organic
4. Uzman, A., Lodish, H., Berk, A., Zipursky, L., & Baltimore, D. (2000). Molecular Cell Biology (4th edition) New York, NY, 2000, ISBN 0-7167-3136-3. Biochemistry and Molecular Biology Education (Vol. 29). https://doi.org/10.1016/S1470-8175(01)00023-6
5. Bruslind, L. (n.d.). 8: Introduction to Viruses - Biology LibreTexts. Retrieved May 18, 2020, from https://bio.libretexts.org/Bookshelves/Microbiology/Book%3A_Microbiology_(Bruslind)/08%3A_Introduction_to_Viruses
6. Viral Replication | Boundless Microbiology. (n.d.). Retrieved May 18, 2020, from https://courses.lumenlearning.com/boundless-microbiology/chapter/viral-replication/
7. Immune responses to viruses | British Society for Immunology. (n.d.). Retrieved May 18, 2020, from https://www.immunology.org/public-information/bitesized-immunology/pathogens-and-disease/immune-responses-viruses
8. Barber, G. N. (2001, April 17). Host defense, viruses and apoptosis. Cell Death and Differentiation. Nature Publishing Group. https://doi.org/10.1038/sj.cdd.4400823
9. Wagner, R. R., & Krug, R. M. (2020, April 15). Virus - Viral DNA integration | Britannica. Retrieved May 18, 2020, from https://www.britannica.com/science/virus/Viral-DNA-integration

The Big Five

10. Harding, A. (2020). The 12 deadliest viruses on Earth. Retrieved May 18, 2020, from livescience.com/56598-deadliest-viruses-on-earth.html
11. Influenza in Animals | Seasonal Influenza (Flu) | CDC. (n.d.). Retrieved May 18, 2020, from https://www.cdc.gov/flu/other/index.html
12. Taubenberger, J. K., & Morens, D. M. (2008). The Pathology of Influenza Virus Infections. Annual Review of Pathology: Mechanisms of Disease, 3(1), 499–522. https://doi.org/10.1146/annurev.pathmechdis.3.121806.154316
13. Samji, T. (2009, December). Influenza A: Understanding the viral life cycle. Yale Journal of Biology and Medicine. Yale Journal of Biology and Medicine.
14. https://www.medicalnewstoday.com/articles/151739.php#prevention
15. Looker, K. J., Magaret, A. S., May, M. T., Turner, K. M. E., Vickerman, P., Gottlieb, S. L., & Newman, L. M. (2015). Global and Regional Estimates of Prevalent and Incident Herpes Simplex Virus Type 1 Infections in 2012. PLOS ONE, 10(10), e0140765. https://doi.org/10.1371/journal.pone.0140765
16. Whitley, R., Kimberlin, D. W., & Prober, C. G. (2007). Pathogenesis and disease. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge University Press.
17. https://www.mayoclinic.org/diseases-conditions/keratitis/symptoms-causes/syc-20374110
18. Dorsal root ganglion - Wikipedia. (n.d.). Retrieved May 18, 2020, from https://en.wikipedia.org/wiki/Dorsal_root_ganglion

19. https://www.mayoclinic.org/diseases-conditions/encephalitis/symptoms-causes/syc-20356136
20. What is Polio? (n.d.). Retrieved May 18, 2020, from https://www.cdc.gov/polio/what-is-polio/index.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fpolio%2Fabout%2Findex.htm
21. Polio en vaccineren | Rijksvaccinatieprogramma.nl. (n.d.). Retrieved May 18, 2020, from https://rijksvaccinatieprogramma.nl/infectieziekten/polio
22. Poliomyelitis. (2019). Retrieved May 18, 2020, from https://www.who.int/en/news-room/fact-sheets/detail/poliomyelitis
23. Alphaviruses - Latest research and news | Nature. (n.d.). Retrieved May 18, 2020, from https://www.nature.com/subjects/alphaviruses
24. Information For Health Care Providers | Chikungunya virus | CDC. (n.d.). Retrieved May 18, 2020, from https://www.cdc.gov/chikungunya/hc/index.html
25. Semliki Forest virus | MSDSonline. (n.d.). Retrieved May 18, 2020, from https://www.msdsonline.com/resources/sds-resources/free-safety-data-sheet-index/semliki-forest-virus/
26. Facts about Sindbis fever. (n.d.). Retrieved May 18, 2020, from https://www.ecdc.europa.eu/en/sindbis-fever/facts
27. Franklinos, L. H. V, Jones, K. E., Redding, D. W., & Abubakar, I. (2019). The effect of global change on mosquito-borne disease. The Lancet Infectious Diseases, 19, e302–e312. https://doi.org/10.1016/S1473-3099(19)30161-6
28. Stein, V. (2019, March 28). How climate change will put billions more at risk of mosquito-borne diseases | PBS NewsHour. Retrieved May 18, 2020, from https://www.pbs.org/newshour/science/how-climate-change-will-put-billions-more-at-risk-of-mosquito-borne-diseases
29. History of HIV and AIDS overview. (2019). Retrieved May 18, 2020, from https://www.avert.org/professionals/history-hiv-aids/overview
30. Global HIV and AIDS statistics. (2020). Retrieved May 18, 2020, from https://www.avert.org/global-hiv-and-aids-statistics
31. Origin of HIV & AIDS. (2019). Retrieved May 18, 2020, from https://www.avert.org/professionals/history-hiv-aids/origin
32. How HIV infects the body and the lifecycle of HIV. (2020). Retrieved May 18, 2020, from https://www.avert.org/about-hiv-aids/how-infects-body
33. HIV/AIDS: The Basics | Understanding HIV/AIDS. (2019). Retrieved May 18, 2020, from https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/19/45/hiv-aids--the-basics

Virus Evolution

34. Wessner, D. R. (2010). Origin of Viruses. Nature Education.
35. Evolution of viruses | Viruses | Khan Academy. (n.d.). Retrieved May 18, 2020, from https://www.khanacademy.org/science/biology/biology-of-viruses/virus-biology/a/evolution-of-viruses
36. SARS (severe acute respiratory syndrome) - NHS. (n.d.). Retrieved May 18, 2020, from https://www.nhs.uk/conditions/sars/
37. Blaser, M. J. (2015). Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plagues - Martin J. Blaser, MD - Google Boeken. Picador.
38. Cliff, A., & Haggett, P. (1984). Island Epidemics. Scientific American, 250(5), 138–147.

Awareness Calendar

39. Usher Syndrome Awareness Day. (n.d.). Retrieved May 18, 2020, from https://www.usher-syndrome.org/take-action/ush-awareness-day.html
40. What is Usher syndrome? (n.d.). Retrieved May 18, 2020, from https://www.usher-syndrome.org/what-is-usher-syndrome/
41. About us | World CP Day. (n.d.). Retrieved May 18, 2020, from https://worldcpday.org/about-us/
42. GERD Awareness Week. (n.d.). Retrieved May 18, 2020, from https://www.aboutgerd.org/gerd-awareness-week.html
43. Introduction to GERD. (n.d.). Retrieved May 18, 2020, from https://www.aboutgerd.org/what-is-gerd/introduction-to-gerd.html
44. International Day of Persons with Disabilities EN | United Nations. (n.d.). Retrieved May 18, 2020, from https://www.un.org/en/observances/day-of-persons-with-disabilities
45. Moebius Syndrome Awareness Day | Moebius Syndrome FoundationMoebius Syndrome Foundation. (n.d.). Retrieved May 18, 2020, from https://moebiussyndrome.org/events/moebius-syndrome-awareness-day/
46. What is Moebius syndrome? | Moebius Syndrome FoundationMoebius Syndrome Foundation. (n.d.). Retrieved May 18, 2020, from https://moebiussyndrome.org/about-moebius-syndrome/what-is-moebius-syndrome/
47. International Epilepsy Day | International Epilepsy Charity. (n.d.). Retrieved May 18, 2020, from https://internationalepilepsyday.org/
48. About Epilepsy | International Epilepsy Day. (n.d.). Retrieved May 18, 2020, from https://internationalepilepsyday.org/about-epilepsy/
49. 2020 WKD Theme - World Kidney Day. (2020). Retrieved May 18, 2020, from https://www.worldkidneyday.org/2020-campaign/2020-wkd-theme/
50. World Hemophilia Day - World Federation of Hemophilia. (n.d.). Retrieved May 18, 2020, from https://www.wfh.org/en/events/world-hemophilia-day
51. WFH eLearning Platform - Inherited Bleeding Disorders. (n.d.). Retrieved May 18, 2020, from https://elearning.wfh.org/elearning-centres/inherited-bleeding-disorders/#bleeding_disorders

History of Vaccination

52. About Edward Jenner — The Jenner Institute. (n.d.). Retrieved May 8, 2020, from https://www.jenner.ac.uk/about/edward-jenner
53. Evans, K. (2017). From variolation to vaccination | Microbiology. Retrieved May 8, 2020, from https://www.labroots.com/trending/microbiology/4928/variolation-vaccination
54. Stern, A. M., & Markel, H. (2020). The History Of Vaccines And Immunization: Familiar Patterns, New Challenges. Health Affairs, 24(3), 611–621. https://doi.org/10.1377/hlthaff.24.3.611
55. Plotkin, S. (2014). History of vaccination. PNAS, 111(34), 12283–12287. https://doi.org/10.1073/pnas.1400472111
56. Gotschlich, E. C., Liu, T. Y., & Artenstein, M. S. (1969). Human immunity to the meningococcus. 3. Preparation and immunochemical properties of the group A, group B, and group C meningococcal polysaccharides. The Journal of Experimental Medicine, 129(6), 1349–1365. https://doi.org/10.1084/jem.129.6.1349
57. Steel, J., & Lowen, A. C. (2014). Influenza a virus reassortment. Current Topics in Microbiology and Immunology, 385, 377–401. https://doi.org/10.1007/82_2014_395
58. Del Tordello, E., Rappuoli, R., & Delany, I. (2017). Reverse Vaccinology: Exploiting Genomes for Vaccine Design. In Human Vaccines: Emerging Technologies in Design and Development (pp. 65–86). Elsevier Inc. https://doi.org/10.1016/B978-0-12-802302-0.00002-9

59. Stevens, H., Goldman, M., Mahoney, R. T., Stevens, P., & Huys, I. (2017). Global Challenges Report - Vaccines: Accelerating Innovation and Access.

Anti-Vaxxers

60. Capurro, G., Greenberg, J., Dube, E., & Driedger, M. (2018). MEASLES, MORAL REGULATION AND THE SOCIAL CONSTRUCTION OF RISK: MEDIA NARRATIVES OF "ANTI-VAXXERS" AND THE 2015 DISNEYLAND OUTBREAK. Canadian Journal of Sociology, 43(1), 25+.
61. Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., … Walker-Smith, J. A. (1998). Retracted: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet, 351(9103), 637–641. https://doi.org/10.1016/S0140-6736(97)11096-0
62. Rao, T. S. S., & Andrade, C. (2011, April). The MMR vaccine and autism: Sensation, refutation, retraction, and fraud. Indian Journal of Psychiatry. Wolters Kluwer -- Medknow Publications. https://doi.org/10.4103/0019-5545.82529
63. Fefferman, N. H., & Naumova, E. N. (2015). Dangers of vaccine refusal near the herd immunity threshold: A modelling study. The Lancet Infectious Diseases, 15(8), 922–926. https://doi.org/10.1016/S1473-3099(15)00053-5
64. Kortum, P., Edwards, C., & Richards-Kortum, R. (2008). The impact of inaccurate Internet health information in a secondary school learning environment. Journal of Medical Internet Research, 10(2). https://doi.org/10.2196/jmir.986
65. Guillemard, M. (2018). Addressing vaccine hesitancy in writing. Medical Writing, 27(1), 39–42.

Antivirals

66. Field, H. J., & De Clercq, E. (2004). Antiviral drugs-a short history of their discovery and development. Microbiology Today, 31(2), 58-61.
67. De Clercq, E., & Li, G. (2016, July 1). Approved antiviral drugs over the past 50 years. Clinical Microbiology Reviews. American Society for Microbiology. https://doi.org/10.1128/CMR.00102-15
68. Virology Lectures 2019 #20: Antivirals - YouTube. (2019). Retrieved May 8, 2020, from https://www.youtube.com/watch?v=w4N63NY_jDc
69. David E. Golan, E. J. (2017). Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Wolters Kluwer.
70. Gentile, I., Viola, C., Borgia, F., Castaldo, G., & Borgia, G. (2009). Telaprevir: A Promising Protease Inhibitor for the Treatment of Hepatitis C Virus Infection. Current Medicinal Chemistry, 16(9), 1115–1121. https://doi.org/10.2174/092986709787581789

Vaccines in Development

71. WHO | Vaccines and diseases. (2019). WHO.
72. WHO | Tracking the New Vaccine Pipeline. (2018). WHO.
73. WHO | WHO vaccine pipeline tracker. (2016). WHO.
74. Safety, Tolerability, and Immunogenicity Study of Homologous Ad26 Mosaic Vector Vaccine Regimens or Heterologous Ad26 Mosaic and MVA Mosaic Vector Vaccine Regimens With Glycoprotein 140 (gp140) for Human Immunodeficiency Virus (HIV) Prevention - Full Text View - ClinicalTrials.gov. (n.d.). Retrieved May 8, 2020, from https://clinicaltrials.gov/ct2/show/study/NCT02315703?term=NCT02315703&rank=1
75. Stephenson, K. E., D'Couto, H. T., & Barouch, D. H. (2016, August 1). New concepts in HIV-1 vaccine development. Current Opinion in Immunology. Elsevier Ltd. https://doi.org/10.1016/j.coi.2016.05.011
76. What is a Mosaic HIV Vaccine and How Does it Work? | Johnson & Johnson. (n.d.). Retrieved May 8, 2020, from https://www.jnj.com/innovation/what-is-a-mosaic-hiv-vaccine

77. Altenburg, A. F., Kreijtz, J. H. C. M., de Vries, R. D., Song, F., Fux, R., Rimmelzwaan, G. F., … Volz, A. (2014, July 17). Modified vaccinia virus ankara (MVA) as production platform for vaccines against influenza and other viral respiratory Diseases. Viruses. MDPI AG. https://doi.org/10.3390/v6072735
78. RTS, & Partnership, S. C. T. (2015). Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: Final results of a phase 3, individually randomised, controlled trial. The Lancet, 386 (9988), 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8
79. Duffy, P. E., Sahu, T., Akue, A., Milman, N., & Anderson, C. (2012). Pre-erythrocytic malaria vaccines: identifying the targets. Expert Review of Vaccines. NIH Public Access. https://doi.org/10.1586/erv.12.92
80. Weekly epidemiological record Relevé épidémiologique hebdomadaire. (n.d.). WHO.
81. Malaria vaccine launched in Kenya: Kenya joins Ghana and Malawi to roll out landmark vaccine in pilot introduction | WHO | Regional Office for Africa. (n.d.). Retrieved May 8, 2020, from https://www.afro.who.int/news/malaria-vaccine-launched-kenya-kenya-joins-ghana-and-malawi-roll-out-landmark-vaccine-pilot
82. WHO | Tuberculosis Vaccines. (2013). WHO.
83. Phase 1 Clinical Trial of the Safety and Immunogenicity of an Adenovirus-based TB Vaccine Administered by Aerosol - Full Text View - ClinicalTrials.gov. (n.d.). Retrieved May 8, 2020, from https://clinicaltrials.gov/ct2/show/NCT02337270?term=Ad5+Ag85A
84. New vaccine against Respiratory Syncytial Virus (RSV) elicits strong immune response -- ScienceDaily. (n.d.). Retrieved May 8, 2020, from https://www.sciencedaily.com/releases/2019/08/190801142608.htm
85. Crank, M. C., Ruckwardt, T. J., Chen, M., Morabito, K. M., Phung, E., Costner, P. J., … Graham, B. S. (2019). A proof of concept for structure-based vaccine design targeting RSV in humans. Science, 365(6452), 505–509. https://doi.org/10.1126/science.aav9033
86. Dose, Safety, Tolerability and Immunogenicity of a Stabilized Prefusion RSV F Subunit Protein Vaccine, VRC-RSVRGP084-00-VP (DS-Cav1), Alone or With Alum Adjuvant, in Healthy Adults - Full Text View - ClinicalTrials.gov. (n.d.). Retrieved May 8, 2020, from https://clinicaltrials.gov/ct2/show/NCT03049488?term=NCT03049488&rank=1

Cancer Vaccines

87. Greenwood, B. (2014, June 19). The contribution of vaccination to global health: Past, present and future. Philosophical Transactions of the Royal Society B: Biological Sciences. Royal Society of London. https://doi.org/10.1098/rstb.2013.0433
88. McCarthy, E. F. (2006). The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. The Iowa Orthopaedic Journal, 26, 154–158.
89. Guo, C., Manjili, M. H., Subjeck, J. R., Sarkar, D., Fisher, P. B., & Wang, X. Y. (2013). Therapeutic cancer vaccines. Past, present, and future. In Advances in Cancer Research (Vol. 119, pp. 421–475). Academic Press Inc. https://doi.org/10.1016/B978-0-12-407190-2.00007-1
90. Wang, L., Pegram, M. D., & Wu, J. C. (2019). Induced pluripotent stem cells as a novel cancer vaccine. Expert Opinion on Biological Therapy, 19(11), 1191–1197. https://doi.org/10.1080/14712598.2019.1650909
91. Drake, C. G., Jaffee, E., & Pardoll, D. M. (2006, January 1). Mechanisms of Immune Evasion by Tumors. Advances in Immunology. Academic Press. https://doi.org/10.1016/S0065-2776(06)90002-9
92. Hollingsworth, R. E., & Jansen, K. (2019, December 1). Turning the corner on therapeutic cancer vaccines. Npj Vaccines. Nature Publishing Group. https://doi.org/10.1038/s41541-019-0103-y
93. Pedersen, S. R., Sørensen, M. R., Buus, S., Christensen, J. P., & Thomsen, A. R. (2013). Comparison of Vaccine-Induced Effector CD8 T Cell Responses Directed against Self- and Non–Self-Tumor Antigens: Implications for Cancer Immunotherapy. The Journal of Immunology, 191(7), 3955–3967. https://doi.org/10.4049/jimmunol.1300555

94. Vormehr, M., Diken, M., Türeci, Ö., Sahin, U., & Kreiter, S. (2020). Personalized neo-epitope vaccines for cancer treatment. In Recent Results in Cancer Research (Vol. 214, pp. 153–167). Springer New York LLC. https://doi.org/10.1007/978-3-030-23765-3_5
95. Larocca, C., & Schlom, J. (2011, September). Viral vector-based therapeutic cancer vaccines. Cancer Journal. Cancer J. https://doi.org/10.1097/PPO.0b013e3182325e63
96. Sprooten, J., Ceusters, J., Coosemans, A., Agostinis, P., De Vleeschouwer, S., Zitvogel, L., … Garg, A. D. (2019, November 2). Trial watch: dendritic cell vaccination for cancer immunotherapy. OncoImmunology. Taylor and Francis Inc. https://doi.org/10.1080/2162402X.2019.1638212
97. Sorensen, M. R., Holst, P. J., Steffensen, M. A., Christensen, J. P., & Thomsen, A. R. (2010). Adenoviral vaccination combined with CD40 stimulation and CTLA-4 blockage can lead to complete tumor regression in a murine melanoma model. Vaccine, 28(41), 6757–6764. https://doi.org/10.1016/j.vaccine.2010.07.066

Latest News

98. Nieuw microscopengebouw bij De Wied | DUB. (n.d.). Retrieved May 8, 2020, from https://www.dub.uu.nl/nl/nieuws/nieuw-microscopengebouw-bij-de-wied
99. Universiteit Utrecht en BAM tekenen overeenkomst voor realisatie Life Sciences Cluster in David de Wiedgebouw | BAM Bouw en Techniek. (n.d.). Retrieved May 8, 2020, from https://www.bambouwentechniek.nl/nieuws/2019/6/universiteit-utrecht-en-bam-tekenen-overeenkomst-voor-realisatie-life-sciences-cluster
100. Life Science Cluster David de Wied | Ector Hoogstad Architecten. (n.d.). Retrieved May 8, 2020, from https://www.ectorhoogstad.com/projects/life-science-cluster-david-de-wied
101. Start bouw Life Science Cluster David de Wiedgebouw. (n.d.). Retrieved May 8, 2020, from https://imdbv.nl/Nieuws/Start-bouw-Life-Science-Cluster-David-de-Wiedgebouw
102. VSNU Nieuwsbericht. (n.d.). Retrieved May 8, 2020, from https://www.vsnu.nl/nl_NL/nieuwsbericht.html/nieuwsbericht/552-dutch-research-institutions-and-elsevier-reach-framework-agreement
103. Ferrari, L., Stucchi, R., Konstantoulea, K., van de Kamp, G., Kos, R., Geerts, W. J. C., … Rüdiger, S. G. D. (2020). Arginine π-stacking drives binding to fibrils of the Alzheimer protein Tau. Nature Communications, 11(1), 1–13. https://doi.org/10.1038/s41467-019-13745-7
104. Rontogianni, S., Iskit, S., Van Doorn, S., Peeper, D. S., & Altelaar, M. (2020). Combined EGFR and ROCK inhibition in triplenegative breast cancer leads to cell death via impaired autophagic flux. Molecular and Cellular Proteomics, 19 (2), 261–277. https://doi.org/10.1074/mcp.RA119.001800

Important Discoveries in the Medical World: Kuru, the "Laughing Death"

105. Liberski, P. P., Sikorska, B., Lindenbaum, S., Goldfarb, L. G., McLean, C., Hainfellner, J. A., & Brown, P. (2012, February). Kuru: Genes, cannibals and neuropathology. Journal of Neuropathology and Experimental Neurology. NIH Public Access. https://doi.org/10.1097/NEN.0b013e3182444efd
106. Imran, M., & Mahmood, S. (2011). An overview of human prion diseases. Virology Journal. https://doi.org/10.1186/1743-422X-8-559
107. Will R. G. (2003). Acquired prion disease: iatrogenic CJD, variant CJD, kuru. British medical bulletin, 66, 255–265. https://doi.org/10.1093/bmb/66.1.255

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