

Vaccines Europe pipeline review 2022

Innovating for tomorrow, today

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Foreword

Vaccines are unique in the value they provide to society.

Since the invention of the smallpox vaccine, vaccines have greatly reduced the prevalence of infectious diseases everywhere in the world and continue to do so. The role of vaccination in addressing the devastating impact of the COVID-19 pandemic is the most recent proof of the value of vaccines and demonstrates the need for a strong and incentivised vaccine research ecosystem.

Vaccination has had a profound impact on our lives since its discovery. Smallpox was eradicated following the World Health Organization (WHO) global vaccination campaign between 1958 and 1977, making it the only human disease to be eradicated. Over the 20th century, with the arrival of new vaccines, successive global elimination plans have been established for many life-threatening and debilitating vaccine-preventable diseases such as poliomyelitis, tetanus, measles and rubella, or more recently different types of bacterial meningitis, pneumonia, sepsis, hepatitis B and related liver cancers, human papillomavirus-related cervical cancers and malaria. Travel vaccines help protect against vaccine-preventable diseases at destination and prevent importation.

Today, there are about 27 infectious diseases, related cancers and use and misuse of antibiotics that can be prevented with vaccines, not only for children but also for adolescents, adults and older adults. Vaccines address significant unmet medical and social needs, contributing to 14 out of the 17 Sustainable Development Goals¹. We would not even want to imagine how the world and its population would look like today without these vaccines.

While vaccines help control, eliminate or eradicate many infectious diseases, there are still those for which no vaccine or treatment has been developed. We also know that the worrying evolution of the climate will generate new disease outbreaks. It is of paramount importance to be prepared for any future challenges as the next health emergency could be right around the corner.

The research-based vaccine industry continues to innovate and develop life-saving vaccines against the threats of today and tomorrow. The review of the pipeline of the 15 member companies of Vaccines Europe reveals 100 new vaccine candidates aiming to tackle these challenges.

However, vaccines solely do not save lives – but vaccination does. Country readiness will also be crucial if we want the EU and global citizens to benefit from the full potential of these vaccines without delay in access.

This first Vaccines Europe pipeline review aims at providing the EU institutions and the Member States visibility on the next generation of vaccines for better preparedness and society resilience-building.



We all have a role to play to ensure everyone can get the vaccines they need.

Sibilia Quilici

Executive Director, Vaccines Europe

Introduction

In recent decades, vaccine innovation has been key to improving public health, increasing the efficiency of healthcare, contributing to socio-economic advancements, and bettering people's quality of life. **However, the global challenges we face today, such as new infectious diseases and climate change, remind us of the need for resilient health systems, environments supportive of innovation, and strong collaboration across all stakeholders.**

The COVID-19 pandemic has highlighted the impact infectious diseases can have on people's health, quality of life, and mortality. It has provided proof of the importance of vaccine innovation for individuals and society at large. The pandemic has also illustrated the connection between health and environment. Failing to protect the environment could make it easier for infectious diseases to arise and spread – especially in the interconnected world we live in today, which can have a devastating impact on human and animal health.

Vaccination is at the heart of the response to the COVID-19 pandemic, saving an estimated 20 million lives in the first year of COVID-19 vaccination programmes².

The development of vaccines in record time was the culmination of decades of research and collaboration within the scientific community.

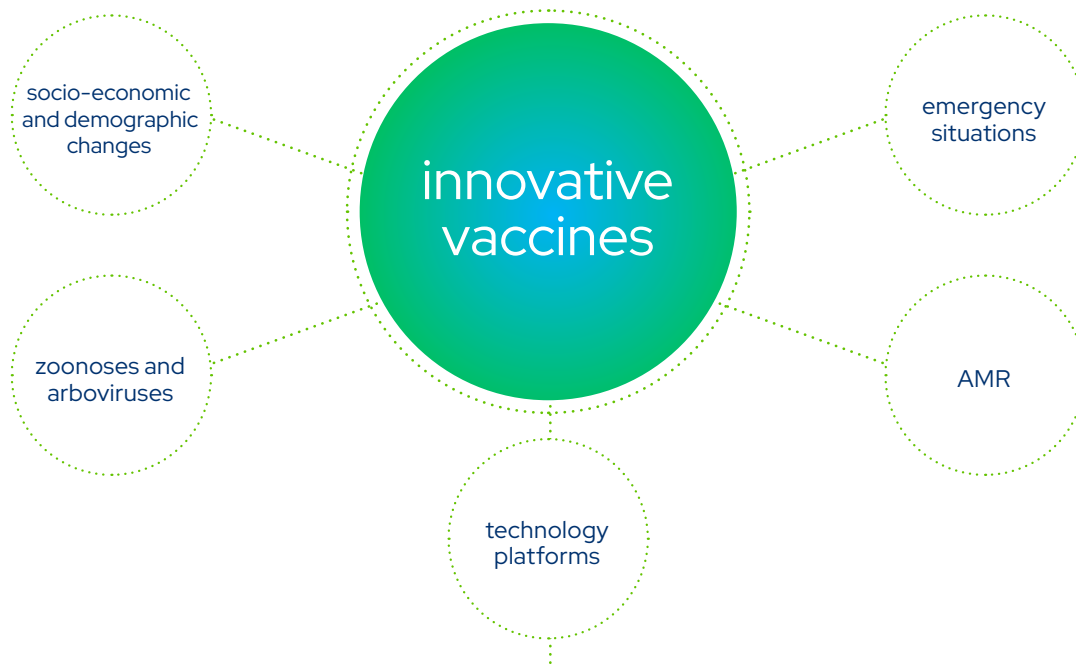
The world was ill-prepared for this pandemic and there are known and possible serious public health threats we must prepare for through innovation across the entire vaccine ecosystem.

Antimicrobial resistance (AMR) is one of the greatest threats of today and the future, as it is expected 10 million people could die every year because of AMR. Additionally, it is projected that AMR could cost up to over \$1 trillion annually by 2050 worldwide³. While we look for effective treatments for AMR, vaccines can contribute to slowing the emergence and spread of drug-resistant bacteria⁴.

COVID-19 vaccination was the first ever adult vaccination campaign rolled-out at global scale. But while some countries were successful in their vaccination campaigns, others still struggle to reach and protect their citizens. Worldwide, people are living longer lives, and as people age their immune systems decline, leading to an increased risk of catching infectious diseases. The immune system is also weakened in pregnancy and in immunocompromised patients, making these populations more susceptible to serious illness.

It is for all the above reasons that adult vaccines are currently being developed. Vaccination for adults, especially for those at higher risk for serious disease, is an important evolution of immunisation strategy and should be a priority for the European and national authorities.

A greater understanding of the immune system and of host–pathogen interactions has allowed for remarkable progress in vaccine design, but there are still many unknowns. New discoveries could accelerate vaccine development and help to address challenging targets. That’s why **innovation and collaboration remain essential to overcoming the challenges of today and tomorrow**, to create healthier lives for people everywhere and address global priorities, such as:



- Developing vaccines to respond to the socio-economic and demographic changes in the European Union and to help build resilient healthcare systems, such as vaccines against Respiratory Syncytial Virus (RSV), group B *Streptococcus* and influenza infections.
- Developing vaccines for emergency situations⁵, like COVID-19, Ebola Virus Disease (EVD), Middle East respiratory syndrome (MERS), Zika virus infection, Nipah virus infection, and henipaviral diseases.
- Developing travel and endemic vaccines for zoonoses or arboviruses, such as dengue fever, chikungunya virus, malaria, and rabies⁶.
- Developing vaccines to slow the emergence and spread of drug-resistant bacteria, such as *Clostridioides difficile*, *Staphylococcus aureus*, *Shigella* spp., extraintestinal pathogenic *Escherichia coli* (ExPEC), and *Streptococcus pneumoniae*.
- Delivering a wide range of vaccine technologies to efficiently tackle emerging and future threats and deliver a diverse portfolio of vaccines that closely match the needs of populations.

Through innovation we can support the diversification of vaccines, providing prescribers with options that enable them to meet people’s needs more closely.

What's in this report?

Vaccines Europe has conducted a pipeline review of its 15 member companies⁷.

Publicly available information was collected and classified based on different criteria. The data was analysed to highlight current trends in the research and development of vaccines, as well as how the vaccines industry helps addressing the challenges of tomorrow. Preclinical development was excluded from this analysis.

The report aims to raise awareness on the importance of scientific innovation in the vaccines ecosystem and to showcase the commitment of vaccine manufacturers to reduce the preventable public health threats, save millions of lives globally and contribute to healthcare and socio-economic resilience. We hope that this report can serve as a first step for horizon-scanning activities by the EU Member States, as well as a basis for early discussions between vaccine developers and health authorities on topics such as value assessment of vaccines, immunisation financing and country readiness. The report is structured around different key topics that represent challenges in the healthcare and health policy fields. Under each section, examples of vaccine candidates from the pipeline of Vaccines Europe members can be found. It should be noted, however, that some vaccine candidates could fit under multiple sections. For an overview of the challenges addressed by these vaccine candidates, please consult the Glossary at the end of the document.

By the end of July 2022, there were 100 vaccine candidates in the pipeline of Vaccines Europe members of which 92 were prophylactic vaccines and 8 were therapeutic vaccines.

Most of the vaccine candidates target infectious diseases caused by viruses, but there are also a significant number targeting bacteria-induced infections. There are also two vaccine candidates against *Plasmodium*, the parasite causing malaria.

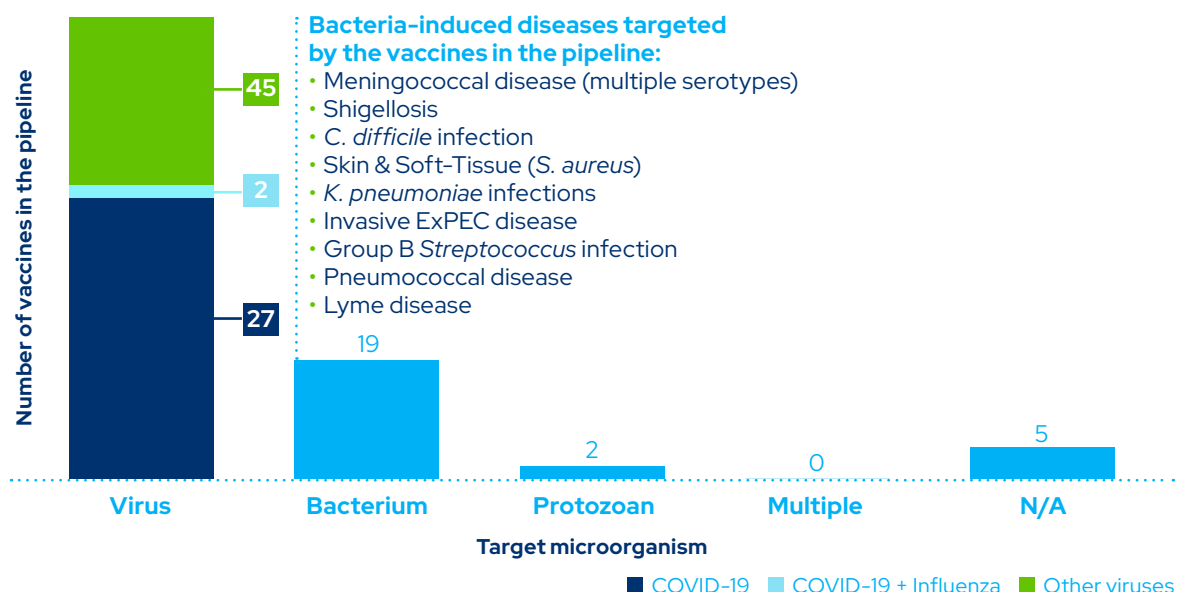


Figure 1. Number of vaccines in the pipeline targeting a specific type of microorganism.

The most frequent targets for the vaccine candidates were COVID-19 (SARS-CoV-2) (29 candidates, including the combination SARS-CoV-2 + influenza), followed by RSV (10 candidates), meningococcal disease (6 candidates), and influenza (11 candidates, including the combination SARS-CoV-2 + influenza). The full overview of the vaccine candidates of Vaccines Europe member companies can be consulted in Figure 2.



Figure 2. Number of vaccine candidates addressing a disease area.

All stages of the clinical development are well represented in the pipelines of the VE members. At the end of July 2022, there were 29 vaccine candidates in Phase III of the clinical trials and 11 under review by the Regulatory Authority. A summary of the vaccines organised by their status of development can be consulted in Annex I.

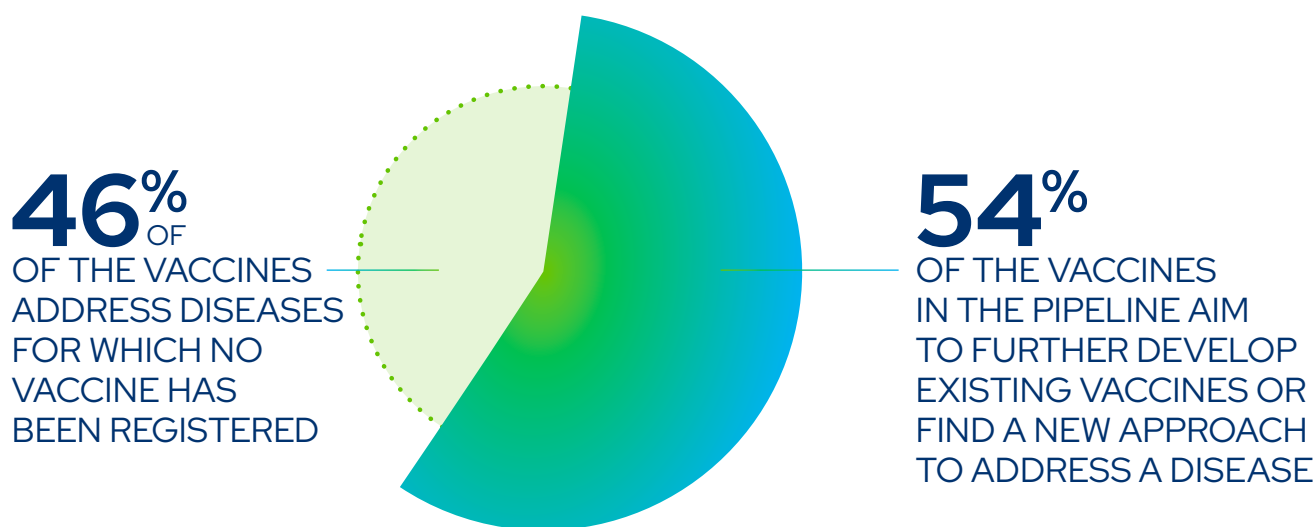


Figure 3. Percentage of vaccines targeting diseases for which there is no registered vaccine vs those further developing existing products.

46% of the vaccine candidates in our members' pipelines aim to address diseases for which no vaccine has been registered until now:

- Chikungunya virus
- Cytomegalovirus
- *Clostridioides difficile* (*C. difficile*)
- Epstein-Barr virus
- Extraintestinal pathogenic *Escherichia coli* (ExPEC)
- Group B *Streptococcus*
- *Herpes simplex* virus
- Human Immunodeficiency Virus (HIV)
- Human metapneumovirus and parainfluenza virus 3
- *Klebsiella pneumoniae* infection
- *Borrelia burgdorferi* (Lyme disease)
- Meningococcal disease (vaccines targeting 5 serotypes - A, B, C, W, Y)
- Nipah virus
- Respiratory Syncytial Virus (RSV)
- *Staphylococcus aureus* (skin and soft tissue infection)
- *Shigella* spp. (Shigellosis)
- Zika virus

	POPULATION	STATUS	PLATFORM
CYTOMEGALOVIRUS (CMV) ^{8, 9, 10} - Cytomegalovirus (CMV) is a common virus for people of all ages, affecting the eyes, lungs, liver, esophagus, stomach, and intestines of people with weakened immune systems. ~60% of adults in developed countries and more than 90% in developing countries infected. - Babies born with congenital CMV infection could lose their hearing. - In the USA, nearly one in three children infected by age five. - Currently, no vaccine available to prevent congenital cytomegalovirus (CMV). Vaccines in the pipeline: 4	 Adults (3) Adults + Older Adults (1)	 Phase I (2) Phase II (1) Phase III (1)	 Protein subunit (1) mRNA (1) Viral Vector (1) Virus-like particle (1)
EPSTEIN-BARR VIRUS (EBV) ^{11, 12} - The first human tumour virus discovered, being strongly involved in the aetiology of multiple lymphoid and epithelial cancers. - EBV is also the primary cause of infectious mononucleosis. - Over 200,000 new EBV-associated cases of cancer and 150,000 deaths worldwide annually. - Up to 70% of adolescents and young adults in developed countries suffer from infectious mononucleosis caused by EBV. - Currently no vaccines or treatments against EBV infection. Vaccines in the pipeline: 1	 Adults (1)	 Phase I (1)	 mRNA (1)
HUMAN IMMUNODEFICIENCY VIRUS (HIV) ¹³ - Major global public health issue, having claimed 36.3 million lives so far. - Attacks the body's immune system, weakening a person's immunity against opportunistic infections (tuberculosis, fungal infections, severe bacterial infections, and some cancers). 37.7 million people living with HIV in 2020, and 680,000 deaths. - No cure for HIV infection but a manageable chronic health condition. Vaccines in the pipeline: 3	 Adults (2) N/A (1)	 Phase I (2) Phase III (1)	 mRNA (2) Viral vector (1)
HUMAN METAPNEUMOVIRUS AND PARAINFLUENZA VIRUS 3 (hMPV/ HPIV3) ^{14, 15, 16} - Human metapneumovirus (hMPV) and Human parainfluenza viruses (HPIVs) can cause upper and lower respiratory disease in people of all ages. 4–16% of all acute respiratory tract infections caused by human metapneumovirus (hMPV). - Human parainfluenza viruses (HPIVs) responsible for around 17% hospitalisation in children less than five years of age due to acute respiratory tract infection. - Currently no vaccines to prevent hMPV or HPIVs, nor specific antiviral therapy. Vaccines in the pipeline: 1	 Paediatric (1)	 Phase I (1)	 mRNA (1)

Vaccine innovation also involves further developing the vaccines that have been available to the population for years or finding new approaches to address a disease area. We refer to this as incremental innovation.

54% of vaccine candidates aim to address the disease areas for which there are already existing vaccines by:

- Improving formulations to increase the convenience for healthcare professionals and patients
- Expanding a vaccine's use to a new population
- Including more target strains in a vaccine
- Developing combination vaccines, which could decrease the number of injections and better fit with national vaccination schedules
- Using a new approach to address a disease (e.g., using a different technology platform, targeting a different part of the antigen)

While all authorised vaccines are safe and effective, Vaccines Europe members are continuously working to improve the benefits/risks knowledge as part of their post authorisation life cycle development.

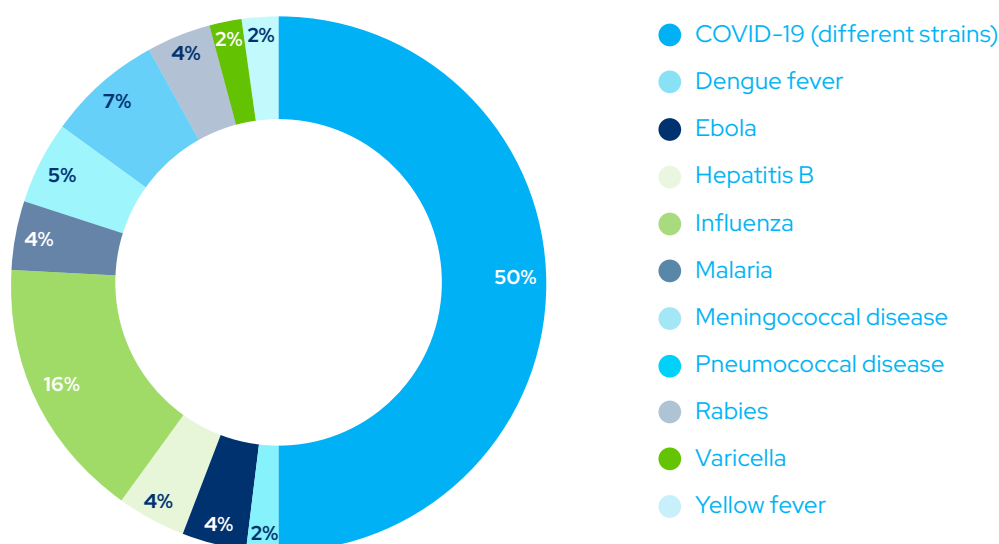


Figure 4. Breakdown of vaccine candidates for diseases for which there is already at least one licensed vaccine.



The vaccines that are currently in the pipeline are covering different types of populations across the lifespan. However, over 80% of them are tested in adults and older adults, reflecting the challenges ahead and the need for a paradigm shift towards a life-course approach to vaccination.

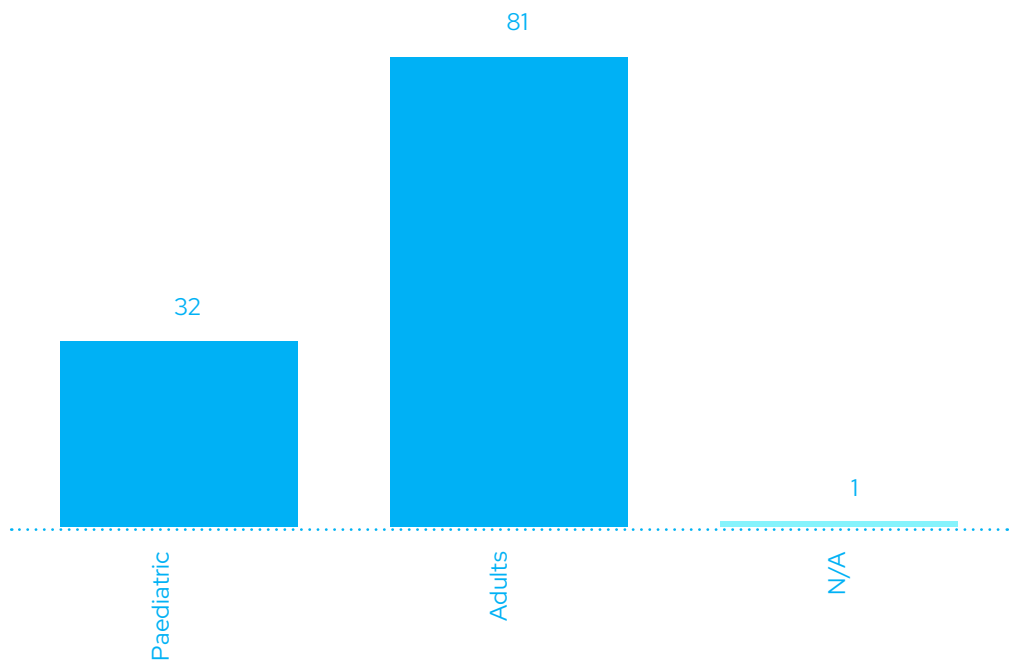


Figure 5a. The number of vaccine candidates tested in each type of population.

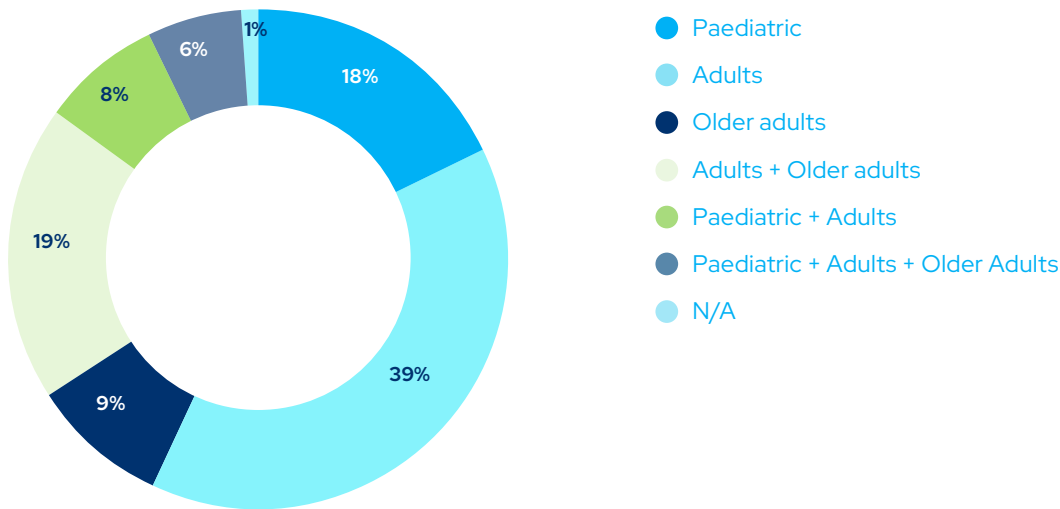


Figure 5b. The number of vaccine candidates tested in each type of population.



ROUTINE VACCINES ACROSS THE LIFESPAN

The life-course approach to vaccination means protecting people at all stages of life. This includes infants, children, adolescents, adults, older adults, pregnant women, people with comorbidities, and people with chronic health conditions.

Childhood vaccination is one of the greatest medical success stories of the 20th century. However, infectious diseases can also have a devastating impact on adults' health, due to the decline of the immune system which makes them more susceptible to infectious diseases. **While paediatric immunisation schedules are well settled throughout Europe, those for adults are not as well established, and vaccination coverage rates are low.**

The COVID-19 pandemic has reinforced that adult immunisation is essential to protect adults against current and future vaccine-preventable diseases and help mitigate potential public health crises. Adult immunisation not only improves quality of life, contributes to healthy aging, and reduces disease, but also offers opportunities to reduce inequalities and increase socio-economic development. The need to extend the benefits of vaccination, from childhood alone to the entire life span, aligns with an increased role prevention plays in healthcare systems.

There are currently 22 vaccines for routine immunisation¹⁷ in our members' pipelines, including vaccines for influenza, varicella, pneumococcal and meningococcal diseases.

Some of them are tested in both paediatric and adult populations. Routine immunisation refers to the vaccination recommended for defined eligible individuals at national or subnational level.

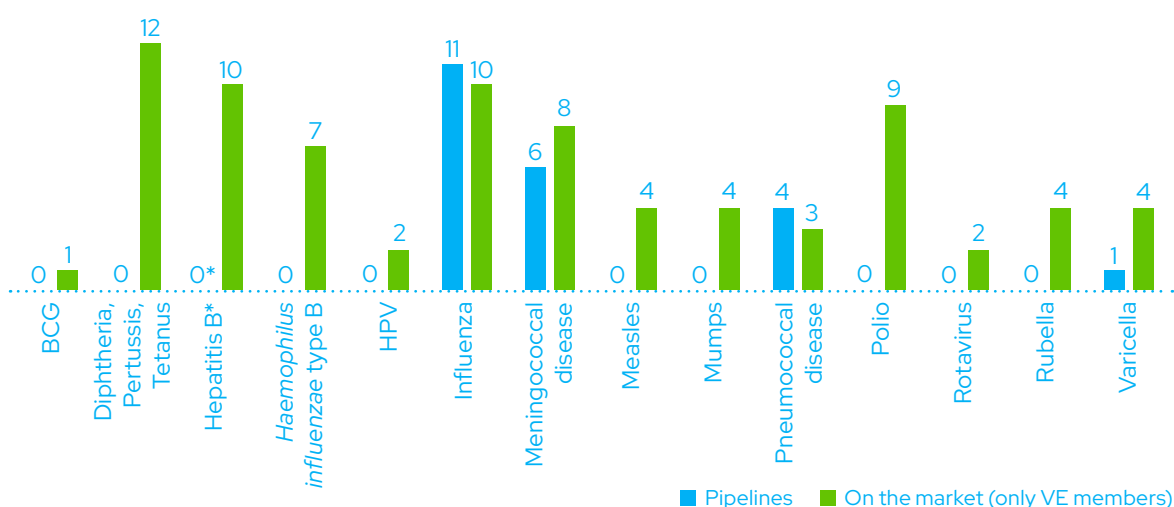


Figure 6. Vaccines in the VE members' pipeline for routine immunisation.

*There are two vaccine candidates against Hepatitis B in the pipeline, however they are intended for therapeutic use and therefore have not been included in this figure.



An important challenge to overcome in the adult population are the respiratory infections responsible for sick leave, hospitalisation and death. For example, seasonal influenza is responsible each year for up to 50 million symptomatic cases in the European Union/ European Economic Area (EU/EEA), and 15,000–70,000 European citizens die of complications associated with influenza. The annual economic and healthcare burden of influenza is substantial, in spite of the usually short duration of illness¹⁸.

It is estimated that yearly seasonal influenza vaccination can save between €248 and €332 million in healthcare costs in Europe by avoiding hospitalisations and visits to general practitioners^{19, 20}.

52 of the vaccine candidates in our members' pipelines target respiratory-transmitted diseases, including coronaviruses, influenza, parainfluenza, and RSV.

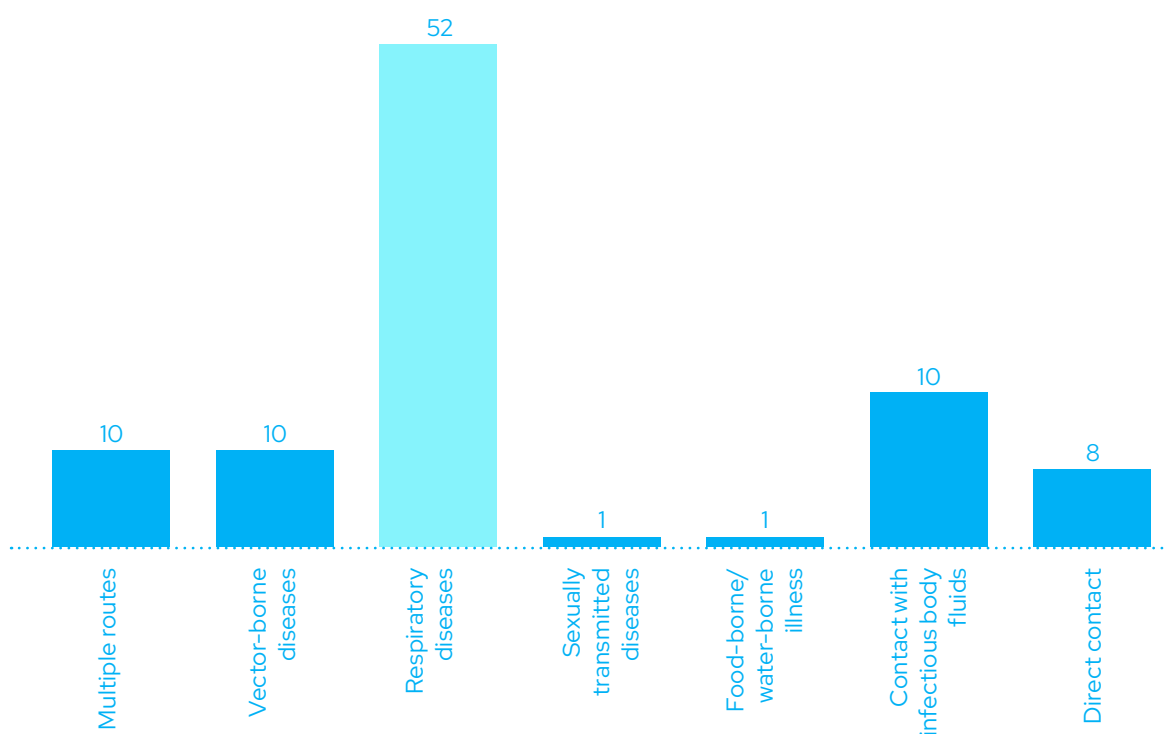


Figure 7. Number of vaccines in development by disease transmission route.

Vaccination has already contributed massively to reduce infant morbidity and mortality worldwide, but more still can be done by using maternal immunisation. For this approach, pregnant women are vaccinated, then the induced antibodies formed are transferred from mother to foetus through the placenta during pregnancy, or after birth in breast milk, providing protection against infections in the first few months of life. Our members' pipelines contain vaccine candidates for maternal immunisation against RSV and group B *Streptococcus* infections.



	POPULATION	STATUS	PLATFORM
GROUP B STREPTOCOCCUS INFECTION (GBS)²¹ - GBS bacteria can cause many types of infections, such as bacteremia and sepsis, bone and joint infections, meningitis, pneumonia, skin and soft-tissue infections. - GBS can cause long-term problems, such as deafness and developmental disabilities in babies. 2 to 3 in every 50 babies (4% to 6%) who develop (GBS) disease die. 10 cases in every 100,000 non-pregnant adults each year. 25 cases in every 100,000 adults 65 years or older each year. - Currently, no licensed vaccine for the prevention of GBS. Vaccines in the pipeline: 1	 Adult*	 Phase II (1)	 Glycoconjugate vaccine (1)
INFLUENZA^{22, 23} - Influenza virus types A and B are both common causes of acute respiratory illnesses, although influenza A viruses are the principal cause of large epidemics, as well as pandemics. - Annual epidemics result in 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths every year. - Severe morbidity and mortality more common among elderly people and in specific high-risk groups. - Influenza viruses undergo frequent changes in their surface antigens, with new influenza outbreaks occurring every year. Vaccines in the pipeline: 9 (influenza) + 2 (influenza + SARS-CoV-2)	 Paediatric (1) Adults (5) Adults + Older Adults (1) Older Adults (2)	 Phase I (5) Phase II (2) Phase III (2)	 mRNA (6) Protein nanoparticles (1) Whole-inactivated virus (2)
MENINGOCOCCAL DISEASE^{24, 25, 26} - Caused by various serogroups of <i>Neisseria meningitidis</i> which one of the most common causes of bacterial meningitis in the world and the only bacterium capable of generating large epidemics of meningitis. - At least 12 serogroups of meningococcus have been characterized; five serogroups cause most of the cases worldwide (A, B, C, Y, W). - In 2018, more than 3,200 confirmed cases of invasive meningococcal disease (IMD), including 324 deaths, reported in 30 EU/EEA countries. - Often a rapid progression of the disease, with an 8–15% case-fatality ratio. This may result in death within one or two days after onset of symptoms. Vaccines in the pipeline: 6**	 Paediatric (4) Paediatric + Adults (1) Paediatric + Adults + Older Adults (1)	 Phase II (2) Phase III (3) Under review (1)	 Protein subunit (2) Glycoconjugate vaccine (3) Combination of a Glycoconjugate vaccine and a protein subunit vaccine (1)



	POPULATION	STATUS	PLATFORM
RSV^{27, 28, 29} - Respiratory Syncytial Virus (RSV) is a globally prevalent cause of lower respiratory tract infection in all age groups. - RSV accounts for hospitalisation of 1 in 5 young children < 5 years diagnosed with acute lower respiratory infections and 1 in 6 in adults > 65 years. - Annually, the virus causes an estimated 118,000 child deaths worldwide. - Currently no licensed vaccines for RSV. Vaccines in the pipeline: 10	 Paediatric (3) Adults (2)* Older Adults (5)	 Phase I (3) Phase II (1) Phase III (6)	 Protein subunit (3) mRNA (2) Viral Vector (1) Live attenuated virus (1) Protein nanoparticles (3)
VARICELLA^{30, 31} - Acute, highly contagious disease caused by varicella-zoster virus (VZV). Following infection, most often in early childhood, the virus remains latent in neural ganglia and can be reactivated later in life to cause herpes zoster, or shingles. Almost one-third of the population will experience an outbreak of shingles during their lifetime. - Varicella is more severe in adults than in children and can be fatal especially in neonates and in immunocompromised individuals. - In the USA, around 4 million annual varicella cases reported with 100–150 deaths and more than 10,000 hospitalisations before the introduction of routine varicella vaccination. Vaccines in the pipeline: 1	 Paediatric + Adults + Older Adults (1)	 Phase II (1)	 Live-attenuated virus (1)

*Maternal immunisation

**3 vaccine candidates against Meningococcal A, B, C, W, Y disease, 2 vaccine candidates against Meningococcal A, C, W, Y disease and 1 vaccine candidate against Meningococcal B disease.



TRAVEL VACCINES

In the 21st century, more people are travelling and migrating than ever before, which contributes to the spread of infectious diseases. Travel vaccines are those recommended to protect people travelling to and from areas with endemics of severe diseases to other parts of the world, and they differ depending on the area of travel.

Vaccination is pivotal in protecting international travellers and preventing the importation of vaccine-preventable diseases, such as cholera, chikungunya virus, dengue fever, hepatitis A, B, and E, Japanese encephalitis, meningococcal disease, polio, rabies, tick-borne encephalitis, typhoid fever, and yellow fever³².

Travel vaccine candidates against chikungunya virus, dengue fever, meningococcal disease, rabies, and yellow fever are currently in development in the pipelines of Vaccines Europe members.

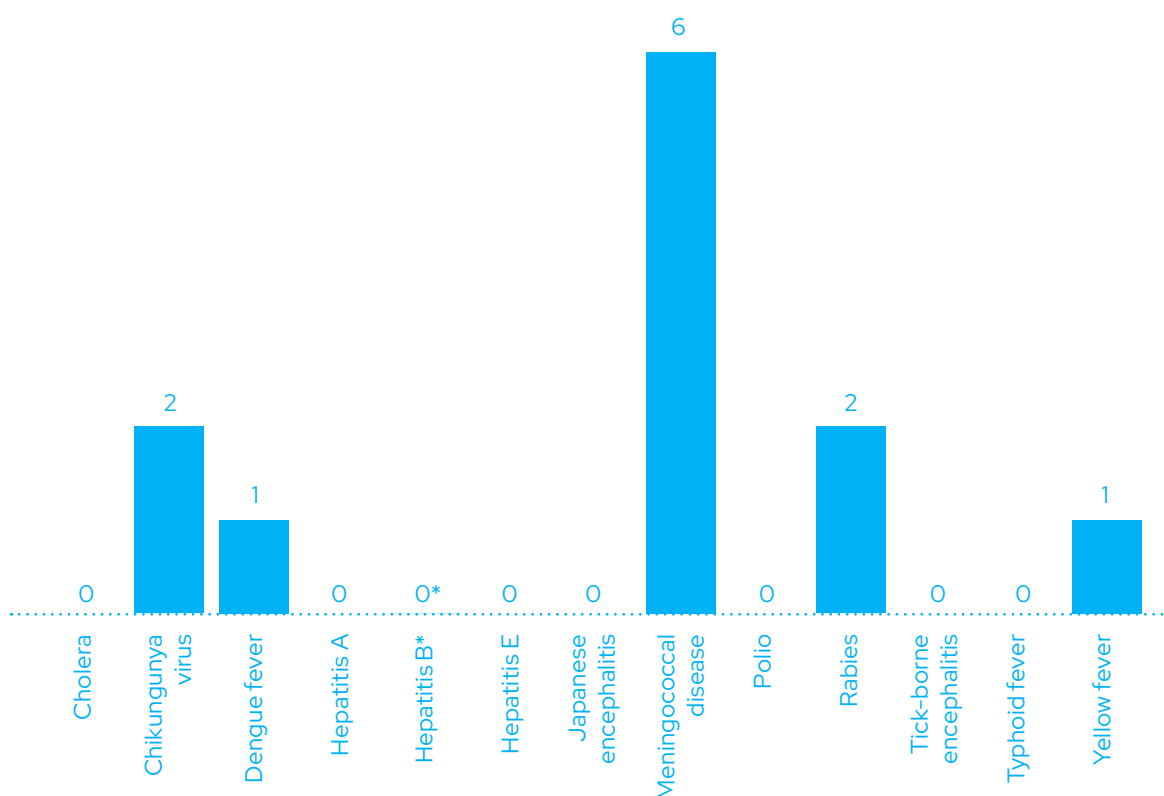


Figure 8. Number of travel vaccines in the pipeline.

*There are two vaccine candidates against Hepatitis B in the pipeline, however they are intended for therapeutic use and therefore have not been included in this figure.



	POPULATION	STATUS	PLATFORM
CHIKUNGUNYA VIRUS ^{33, 34, 35} • Viral disease caused by the chikungunya virus transmitted to humans by infected mosquitoes. • Over 214,000 reported cases by 27th of July 2022 and more than 40 deaths. • Over 106,000 disability-adjusted life years (DALYs) lost on average annually from 2010 to 2019 due to chikungunya infection. • Currently no vaccine or specific drug against the virus. Vaccines in the pipeline: 2	 Adults (2)	 Phase II (1) Phase III (1)	 Viral Vector (1) Live-attenuated virus (1)
DENGUE FEVER ^{36, 37, 38} • Tens of millions of cases each year, resulting in approximately 20,000–25,000 deaths mainly in children. • By far the most important mosquito-borne viral disease affecting humans worldwide. Vaccines in the pipeline: 1	 Paediatric + Adults (1)	 Under review (1)	 Live-attenuated virus (1)
YELLOW FEVER ^{39, 40} • Acute viral haemorrhagic disease transmitted by infected mosquitoes. • 200,000 cases and 30,000 deaths each year, with 90% occurring in Africa. • 20% to 50% of infected persons who develop severe disease die. Vaccines in the pipeline: 1	 Paediatric + Adults + Older Adults (1)	 Phase II (1)	 Live-attenuated virus (1)



ANTIMICROBIAL RESISTANCE

Drug-resistant infections are already common, resulting in longer hospital stays and higher medical costs, as well as increased mortality.

By 2050, 10 million people could die every year because of antimicrobial resistance (AMR). It is projected that AMR could cost up to over \$1 trillion annually by 2050 worldwide⁴¹.

Vaccines are a key tool in the fight against AMR. They are effective before bacteria start to multiply and before different tissues and organs are affected, decreasing the likelihood of resistant mutations spreading.

Available evidence demonstrates that the introduction of the pneumococcal conjugate vaccine in the USA has resulted in an 84% reduction in an invasive disease caused by drug-resistant *Streptococcus pneumoniae* in children under two years of age⁴².

Vaccines Europe members are addressing the challenge of AMR by developing vaccines for *Klebsiella pneumoniae*, *C. difficile*, *Staphylococcus aureus*, *Shigella* spp., Extraintestinal pathogenic *Escherichia coli*, and *Streptococcus pneumoniae*.

There are currently 11 vaccine candidates in our members' pipelines that are targeting antibiotic-resistant bacteria on the WHO's Priority Pathogens list⁴³.

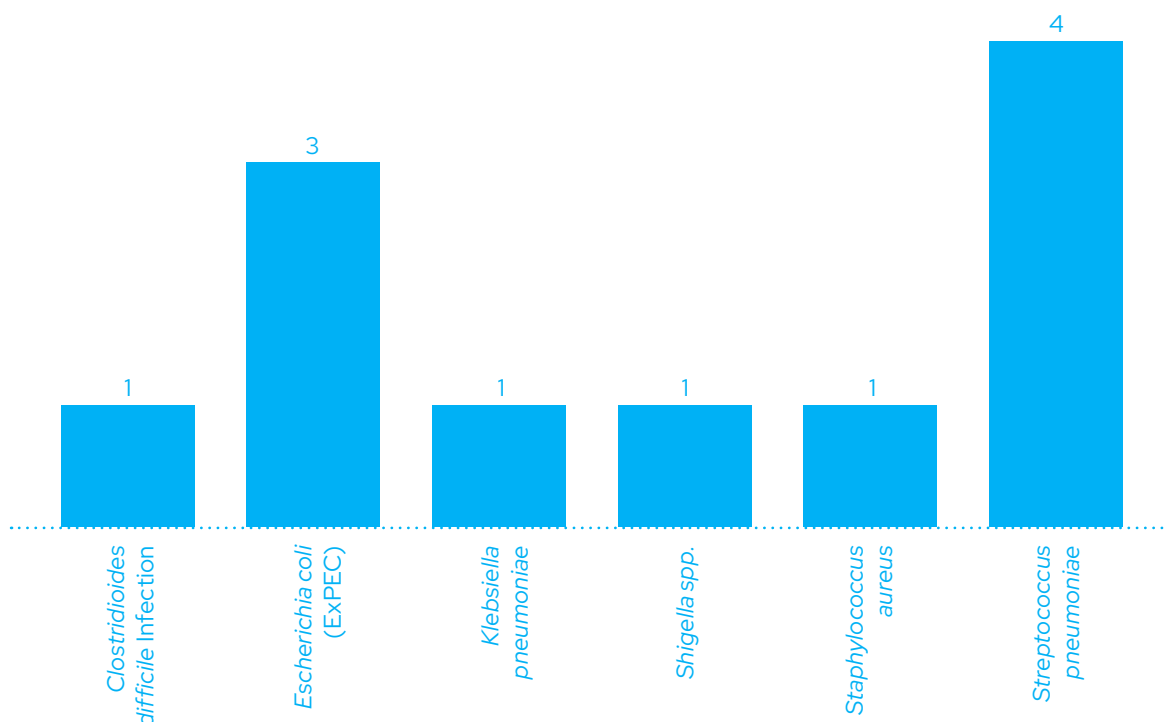


Figure 9. Number of vaccine candidates addressing antibiotic-resistant microorganisms.



Vaccines that prevent viral infections play an important role as well in decreasing the presumptive and inappropriate antibiotic use, either by reducing the erroneous prescriptions that encourage the treatment of viral diseases with antibiotics, or by preventing the associated secondary bacterial superinfections⁴⁴. There is increasing evidence showing the reduction of antibiotic use due to the vaccination against influenza and varicella^{45, 46, 47}. Vaccines against RSV and Human metapneumovirus and parainfluenza virus 3 (hMPV/HPIV-3) are expected to have a considerable impact as well. A recent study showcased that administering an RSV vaccine to pregnant mothers would reduce antimicrobial prescribing among their infants by 12.9% over the first 3 months of life⁴⁸. There is also evidence that vaccination against dengue could reduce the rate of evolution of antibiotic resistance in a scenario of antibiotic misuse in dengue patients⁴⁹. A similar trend is expected for Coronavirus disease, considering the data pointing to the misuse of antibiotics during the pandemic. For example, evidence shows that while antibiotics are used in 75% of the patients suffering from severe COVID-19 in Europe, only 15% of those patients actually develop bacterial superinfections⁵⁰.

	POPULATION	STATUS	PLATFORM
CLOSTRIDIODES DIFFICILE ^{51, 52} - Nearly 124,000 healthcare-associated <i>C. difficile</i> infections (CDIs) annually in acute care hospitals in the EU/EEA, and 3,700 deaths. 1 in 11 people over age 65 diagnosed with a healthcare-associated CDI die within one month. - Currently no licensed vaccine for the prevention of CDI. Vaccines in the pipelines: 3	 Adults + Older Adults (2) Older Adults (1)	 Phase I (1) Phase II (1) Phase III (1)	 Toxoid vaccine (1) Protein subunit (2)
EXTRAIESTINAL PATHOGENIC ESCHERICHIA COLI (EXPEC) ^{53, 54, 55, 56} - Accounts for 70–95% of community-onset urinary tract infections (UTIs) and approximately 50% of nosocomial UTIs. - Leading cause of adult sepsis and bacteremia and the second most common cause of neonatal meningitis. - Great impact on public health and economic burden due to high incidence of ExPEC infections and its antimicrobial resistance. Vaccines in the pipeline: 1	 Older Adults (1)	 Phase III (1)	 Glycoconjugate vaccine (1)
KLEBSIELLA PNEUMONIAE ^{57, 58} - Bacteria that can cause community-acquired and hospital-acquired infections (pneumonia, bloodstream infections, wound or surgical site infections, and meningitis) - Percentage of <i>Klebsiella pneumoniae</i> resistant to a type of antibiotics called carbapenems slowly increased from 8% in 2014 to 10% in 2020. Vaccine in the pipelines: 1	 Adults + Older Adults (1)	 Phase I (1)	 Glycoconjugate vaccine (1)



	POPULATION	STATUS	PLATFORM
SHIGELLOSIS^{59, 60} - Gastrointestinal infection caused by one of four species of <i>Shigella</i>. 77,000 antibiotic-resistant <i>Shigella</i> infections estimated in the USA each year. - Over 6,300 confirmed shigellosis cases in 2017 in 30 EU/EEA countries. Vaccines in the pipeline: 1	 Paediatric + Adults (1)	 Phase II (1)	 Glycoconjugate vaccine (1)
STAPHYLOCOCCUS AUREUS^{61, 62} <i>Staphylococcus aureus</i> (<i>S. aureus</i>) infections common both in community-acquired and hospital-acquired settings. - Treatment remains challenging due to the emergence of multi-drug resistant strains such as MRSA (Methicillin-Resistant <i>Staphylococcus aureus</i>). - Skin and soft tissue infections range in severity from minor, self-limiting, superficial infections to life-threatening invasive infections such as bacteraemia and osteomyelitis. Vaccines in the pipelines: 1	 Adults (1)	 Phase II (1)	 Glycoconjugate vaccine (1)
STREPTOCOCCUS PNEUMONIAE^{63, 64} <i>Streptococcus pneumoniae</i> (<i>S. pneumoniae</i>) is the leading cause of community-acquired pneumonia. - Incidence of community-acquired pneumonia caused by <i>S. pneumoniae</i> is 1 in 1,000 adults per year. 1 million children die of pneumococcal disease every year. - Pneumococcal resistance to antimicrobials is a serious and rapidly increasing problem worldwide. Vaccines in the pipeline: 4	 Paediatric (2) Adults (1) Paediatric + Adults + Older Adults (1)	 Phase II (3) Phase III (1)	 Protein subunit (1) Glycoconjugate vaccine (3)



THERAPEUTIC VACCINES

Therapeutic vaccines are a field still in its infancy compared to preventive vaccines. They work by utilising a patient's own immune system to fight an existing disease or infection, rather than immunising for prevention of a future disease. The aim of therapeutic vaccination is therefore to boost or redirect the immune response and help to clear the disease. There are a wide variety of technology platforms considered for the development of therapeutic vaccines, including mRNA, protein subunits, virus-like particles, and viral vector vaccines that are either co-administered or sequentially administered with adjuvanted recombinant protein vaccines.

Vaccines to treat infectious diseases:

Therapeutic vaccines against infectious diseases aim to activate the patient's immune system to fight and control or ideally eliminate an already established infectious pathogen.

Currently, there are few therapeutic vaccines in the pipelines of the Vaccines Europe companies against hepatitis B and *Herpes simplex* virus.

	POPULATION	STATUS	PLATFORM
HEPATITIS B⁶⁵ - Viral infection that attacks the liver and can cause both acute and chronic disease. 296 million people living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. - Estimated 820,000 deaths in 2019, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer). Vaccines in the pipeline: 2	 Adults (2)	 Phase II (2)	 Viral vector vaccine co- or sequentially administrated with adjuvanted recombinant proteins vaccine (1) Virus-like particle (1)
HERPES SIMPLEX VIRUS (HSV)^{66, 67} 2 types of HSV: HSV-1 and HSV-2. They can cause oral herpes (HSV-1), genital herpes (HSV-1 and HSV-2) and eye infection leading to blinding complications (HSV-1 and HSV-2). 3.7 billion people under age 50 (67%) with HSV-1 infection globally. 491 million people aged 15–49 (13%) worldwide with HSV-2 infection. - Similar to Varicella Zoster Virus, latent HSV infection can re-activate and lead to recurrent outbreaks of symptoms. Vaccines in the pipeline: 1	 Adults (1)	 Phase I (1)	 N/A (1)

Vaccines against cancer

When it comes to this type of vaccine, there are two main approaches to be considered. The first one is a prophylactic approach and refers to the prevention of infection-related cancers, such as the liver cancer that could be a consequence of the hepatitis B infection, those related to infection with HPV (Human Papillomavirus) or the Epstein-Barr virus.

The other approach is a curative one. The goal of therapeutic cancer vaccines is to induce tumour regression, eradicate minimal residual disease, establish lasting antitumour memory



and avoid non-specific or adverse reactions⁶⁸. The development of vaccines for the treatment of cancer is challenging, as the vaccine intervention must combat an immune system that has been restrained by mechanisms that sustain the disease in an attempt at self-tolerance⁶⁹. However, recent results from ongoing clinical trials for such vaccines are promising.

There are five vaccines in Vaccines Europe members' pipelines against different types of cancers, such as glioblastoma, lung, colorectal, pancreatic and skin cancer, as well as solid tumour.

	POPULATION	STATUS	PLATFORM
GLIOBLASTOMA⁷⁰ - Fast-growing and aggressive brain tumour that can result in death in six months or less, if untreated. - Incidence of 3.21 per 100,000 population. - GBM presents unique treatment challenges due to the localisation of tumours in the brain. - Approximately 40% survival in the first year post-diagnosis and 17% in the second year. Vaccines in the pipeline: 1	 Adults + Older Adults (1)	 Phase II (1)	 Virus-like particle (1)
LUNG, COLORECTAL, PANCREATIC CANCER⁷¹ - Lung cancer - The 2nd most common cancer worldwide - More than 2.2 million new cases of lung cancer in 2020 - Colorectal cancer - The 3rd most common cancer worldwide - More than 1.9 million new cases of colorectal cancer in 2020 - Pancreatic cancer: - The 12th most common cancer worldwide - More than 495,000 new cases of pancreatic cancer in 2020 Vaccines in the pipeline: 1	 Adults (1)	 Phase I (1)	 mRNA (1)
SKIN CANCER^{72, 73, 74} - Most common type of cancer. - The main types of skin cancer are squamous cell carcinoma, basal cell carcinoma, and melanoma. Most deaths from skin cancer are caused by melanoma. - More than 150,000 new cases of melanoma in 2020. \$8.1 billion annual cost of treating skin cancers in the USA. Vaccines in the pipeline: 1	 Adults + Older Adults (1)	 Phase II (1)	 mRNA vaccine (1)
SOLID TUMOUR⁷⁵ - Approximately 90% of adult human cancers. They can develop in many parts of the human body. - Solid tumours can be either non-cancerous (benign), pre-malignant (cells that have the potential to become malignant), or malignant (cancerous). Vaccines in the pipeline: 2	 Adults + Older Adults (2)	 Phase I (2)	 mRNA vaccine (1) Protein subunit (1)

Addressing global health threats



CLIMATE CHANGE

Climate change is having a serious effect on global health. Warming temperatures and increased rainfall can result in mosquitos expanding beyond their existing geographical range, resulting in an increased risk of diseases like West Nile fever, Zika, dengue fever, chikungunya, and malaria. Disruption to the habitats of bats, rodents, and primates can drive these animals to areas where humans are living, making zoonotic exposures more likely.

Storms and floods can lead to wastewater overflow, causing a rise in cholera, noroviruses, and rotavirus. Melting ice and thawing permafrost can expose ancient deadly pathogens, such as anthrax.

Climate change can also impact human behaviour. Extreme weather, such as heatwaves and heavy rainfall, can drive people to cluster together indoors more often, making it easier for infectious diseases to spread. In addition, as humans adapt to changes in temperature, our immune systems can be weakened, making us more vulnerable to respiratory diseases like influenza.

A report issued by the World Bank in 2021 describes how climate change could force 216 million people to migrate within their own countries by 2050⁷⁶, due to the impact on their livelihoods and loss of liveability in highly exposed locations. It is vital that we prepare now for the cross-border health threats posed by climate change.

	POPULATION	STATUS	PLATFORM
MALARIA⁷⁷ - Life-threatening disease caused by <i>Plasmodium</i> parasites that are transmitted to people through the bites of infected female mosquitoes. - Left untreated, malaria can progress to severe illness and death within a period of 24 hours. - In 2020, 241 million cases of malaria worldwide and 627,000 deaths. - In 2020, 95% of malaria cases and 96% of malaria deaths occurred in the WHO African Region. Children under five accounted for about 80% of all malaria deaths in the Region. Vaccines in the pipeline: 2	 Paediatric (1) Paediatric + Adults (1)	 Phase II (2)	 Protein subunit (1) Protein nanoparticles (1)
ZIKA^{78, 79, 80} - Disease caused by a virus transmitted primarily by infected mosquitoes. - Over 707,000 Zika virus disease cases reported in the Americas in 2015–2016. - Infection during pregnancy is associated with complications such as preterm birth and miscarriage or can cause infants to be born with microcephaly and other congenital malformations. - An increased risk of neurologic complications is associated with Zika virus infection in adults and children. - Currently no licensed vaccines or treatments for Zika. Vaccines in the pipeline: 3	 Paediatric + Adults (1) Adults (2)	 Phase I (2) Phase II (1)	 mRNA (1) Whole-inactivated virus (2)



ZOONOSSES AND PANDEMIC PREPAREDNESS

Zoonotic diseases are those transmitted from animals to humans.

It is estimated that 60% of infectious diseases in humans can be attributed to animal origin. Many of these diseases have high mortality rates and the potential to cause epidemics and pandemics. Zoonotic diseases are responsible for approximately 2.7 million deaths and 2.5 billion human illnesses annually, in addition to impacting livestock production and food security⁸¹.

COVID-19 is believed to have originated in animals. Monkeypox, avian influenza, and several other viruses carrying zoonotic infection potential circulating in farmed and wild animals, are a constant reminder that another pandemic could be around the corner.

Vaccines Europe members are addressing the challenge of zoonotic diseases by researching vaccines against coronaviruses (MERS-CoV, SARS-CoV-2), influenza, Ebola, rabies, Lyme disease, Nipah virus disease, yellow fever, malaria, dengue fever, and chikungunya.

The COVID-19 pandemic has stressed the need to strengthen the One Health approach, which focuses on the interconnectivity between the health of human communities, animals, and the environment. This will require strong transdisciplinary collaboration across the sciences. A joint report issued by ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency), and OECD (Organisation for Economic Co-operation and Development) in March 2022 showcased that a One Health approach is essential for the future of animal and public health⁸².



	POPULATION	STATUS	PLATFORM
CORONAVIRUSES INFECTIONS ^{83, 84, 85} - Most coronaviruses infect animals (i.e., birds and mammals – bats and pangolins), which act as reservoirs and intermediate hosts, but can sometimes change host and infect humans. - There are currently seven coronaviruses known to infect humans, four of them causing mild-to-moderate disease and three of them cause more severe and possibly even fatal disease (SARS-CoV, MERS-CoV, SARS-CoV-2) - MERS-CoV: from 2012 to June 2022, over 2,500 confirmed cases, with a death rate of 34.5%. - SARS-CoV2 (COVID-19): over 157 million cases and more than 1.1 million deaths reported in the EU. Vaccines in the pipeline: 28 (coronaviruses)* + 2 (influenza + SARS-CoV-2)	 Adults (12) Adults + Older Adults (10) Paediatric (6) Paediatric + Adults (1) Paediatric + Adults + Older Adults (1)	 Phase I (6) Phase II (6) Phase III (10) Under review (8)	 Viral vector (4) mRNA (18) Protein nanoparticles (3) Protein subunit (2) Virus-like particle (3)
EBOLA VIRUS DISEASE ^{86, 87} - Ebola virus disease is a rare but severe, often fatal illness in humans. - Over 28,000 cases and 11,000 deaths in the largest reported outbreak from 2014 to 2016. - Average fatality rate around 50% (varying from 25% to 90% in past outbreaks). Vaccines in the pipeline: 2	 Paediatric + Adults (1) Adults (1)	 Phase I (1) Under review(1)	 Viral Vector (1) Glycoconjugate vaccine (1)
LYME DISEASE ^{88, 89} - Caused by the bacterium <i>Borrelia burgdorferi</i> and transmitted to humans by the bite of infected ticks. - Around 476,000 cases diagnosed and treated per year in the USA, and over 200,000 cases per year in Western Europe. - If left untreated, infection can spread to joints, the heart, and the nervous system. - Currently no vaccine available. Vaccines in the pipeline: 1	 Paediatric + Adults (1)	 Phase III (1)	 Protein subunit (1)
NIPAH VIRUS INFECTION ^{90, 91} - Estimated fatality rate 40% to 75%. 639 human cases of Nipah virus infection reported from Bangladesh, India, Singapore, Philippines and Malaysia, with a mortality rate of about 59% until 2018. - Fruit bats are the wildlife reservoir of Nipah virus. - Currently no treatment or vaccine available against Nipah virus. Vaccines in the pipeline: 1	 Adults (1)	 Phase I (1)	 mRNA (1)
RABIES ^{92, 93} - Viral disease that causes tens of thousands of deaths every year, mainly in Asia and Africa. - Dogs are the main source of human rabies deaths, contributing up to 99% of all rabies transmissions to humans. - Estimated global cost of US\$ 8.6 billion per year. Vaccines in the pipeline: 2	 Adults (1) Paediatric + Adults + Older Adults (1)	 Phase I (1) Phase III (1)	 mRNA (1) Whole inactivated virus(1)

*1 vaccine candidate against MERS-CoV and 27 against SARS-CoV-2

Technology platforms



Vaccine manufacturing has evolved over the years to overcome limitations and reflect technological advancements.

The pipeline review revealed that the technology used for the most vaccine candidates is mRNA. However, all other technologies are well represented and equally important. **Diversification of vaccine technologies is key to addressing a range of diseases, as different technologies address different pathogens. It also ensures patients are provided with a choice of vaccines to meet their needs.**

Combination vaccines is an approach that has been used for many years in routine immunisation, for example MMR (measles, mumps, rubella) and DTaP (diphtheria, tetanus, acellular pertussis). It's a valuable tool for reducing the number of injections needed to protect against multiple diseases and for better fitting the vaccination schedule. Several types of combination vaccines are currently under development, such as SARS-CoV-2 + influenza and human metapneumovirus + parainfluenza virus 3.

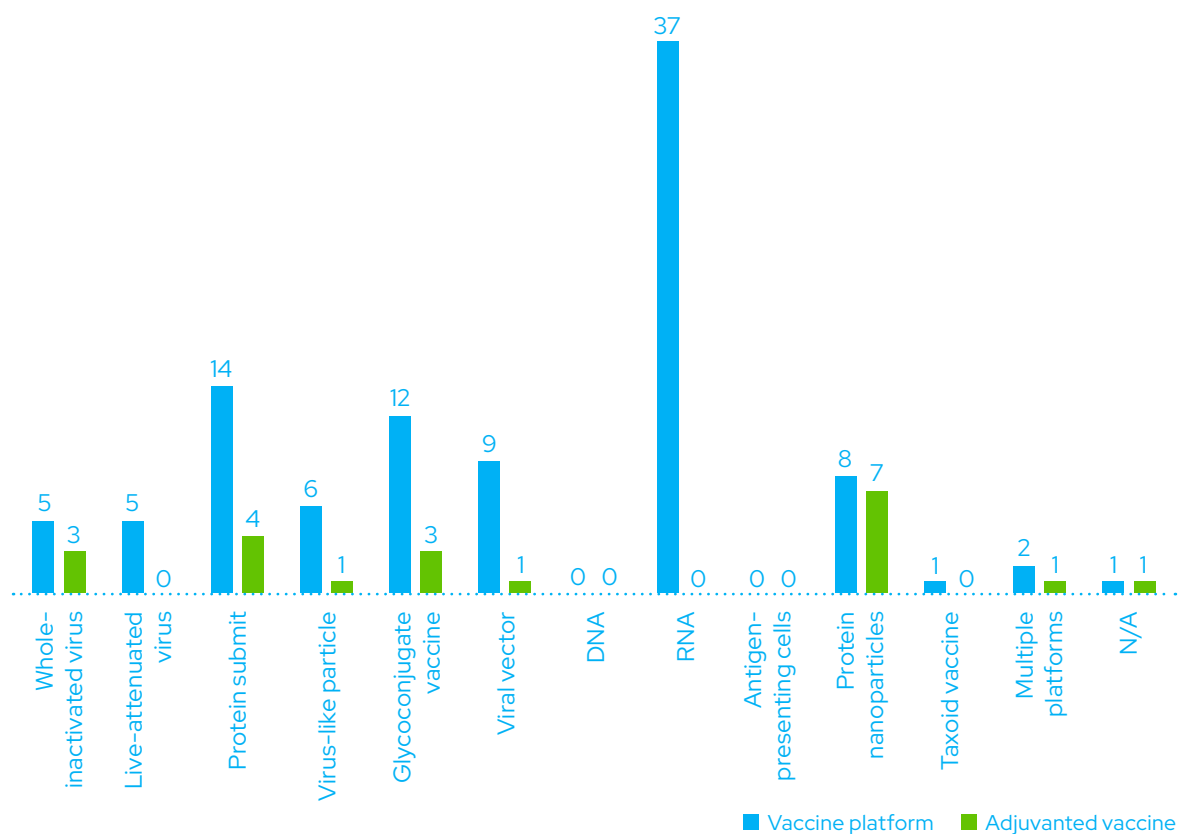


Figure 10. Number of vaccines in development by technology platform.

Conclusion

We need to adopt a life-course approach to vaccination to ensure all people have protection against vaccine-preventable diseases. Vaccines are critical to meeting health goals, to improve the efficiency of healthcare systems, support socio-economic progress, and address the serious cross-border health threats of the future. The innovative pharmaceutical industry has developed, and continues to develop, vaccines to support these goals.

The research and development of vaccines is a very lengthy and costly process due to the high complexity of the products. Yet, pharmaceutical companies don't give up on their quest of developing and supplying vaccines for us, for our families, for our friends, for the entire population. The value of vaccines goes beyond the characteristics of a specific product, having a crucial socio-economic impact. By preventing the onset of a broad spectrum of infectious diseases, vaccines save millions of lives every year.

The pipelines of Vaccines Europe member companies represent a profound testimony of the value of the pharmaceutical industry in addressing many challenges of today and tomorrow, such as health emergency situations, zoonoses and arboviruses, antimicrobial resistance, socio-economic and demographic changes as well as the dangers posed by the climate change.

As showcased in this report, companies are working round the clock to develop and perfect a wide range of vaccine technologies to efficiently tackle emerging and future threats and deliver a diverse portfolio of vaccines that closely match the needs of populations.

But getting a vaccine from the lab to the population is a collaborative effort. Everyone has a role to play in ensuring that vaccines reach the people who need them: from discovery in academia, biotech or pharma, to clinical development, to the European Medicines Agency (EMA) and regulators who review and approve new vaccines, to the National Immunisation Technical Advisory Groups (NITAGs) and Health Technology Assessment (HTA) bodies that assess them, to the governments providing funding, infrastructure and campaigns to support immunisation programmes, to the healthcare providers who inform patients, answer questions and administer the vaccines.

To allow continuous innovation to happen, we need a dynamic and well-funded research ecosystem in Europe, that provides regulatory flexibilities and a supportive intellectual property framework. We must also improve market access pathways for vaccine assessments, by improving timelines, inclusiveness, consistency, and transparency of assessments. Moreover, it is important to strengthen national immunisation programmes through continuous dialogue with NITAGs and governments, implement early horizon-scanning to ensure sustainable funding for prevention across the EU countries, build the necessary infrastructure for adult immunisation programmes, improve vaccination coverage rates, and ensure their timely monitoring throughout Europe.

We must prepare for tomorrow, today.

ANNEX I – Summary of vaccine candidates organised based on the stage of the clinical development

DISEASE	NUMBER OF VACCINE CANDIDATES	TRIAL POPULATION		
		PAEDIATRIC	ADULTS	OLDER ADULTS
PHASE I CLINICAL TRIALS				
<i>Clostridioides difficile</i> infection	1		✓	✓
COVID-19	4		✓	
COVID-19 + Influenza	1		✓	✓
Cytomegalovirus	2		✓	
Ebola	1		✓	
Epstein-Barr virus infection	1		✓	
<i>Herpes simplex</i> virus*	1		✓	
Human immunodeficiency virus (HIV)	2		✓	
Human metapneumovirus and parainfluenza virus 3 (hMPV/PIV3)	1	✓		
Influenza	5		✓	✓
<i>Klebsiella pneumoniae</i>	1		✓	✓
Lung/Colorectal/Pancreatic cancer*	1		✓	
Middle-East Respiratory Syndrome (MERS)	1		✓	
Nipah virus	1		✓	
Rabies	1		✓	
Respiratory Syncytial Virus	3	✓		✓
Solid tumour*	2		✓	✓
Zika	2	✓	✓	

DISEASE	NUMBER OF VACCINE CANDIDATES	TRIAL POPULATION		
		PAEDIATRIC	ADULTS	OLDER ADULTS
PHASE II CLINICAL TRIALS				
Chikungunya virus	1		✓	
<i>Clostridioides difficile</i> infection	1			✓
COVID-19	5		✓	✓
COVID-19 + Influenza	1		✓	
Cytomegalovirus	1		✓	✓
Glioblastoma*	1		✓	✓
Group B Streptococcus Infection**	1		✓	
Hepatitis B*	2		✓	
Influenza	2	✓	✓	✓
Malaria	2	✓	✓	
Meningococcal disease (B and A, B, C, W, Y)	2	✓	✓	✓
Pneumococcal disease	3	✓	✓	✓
Respiratory Syncytial Virus	1	✓		
Shigellosis	1	✓	✓	
Skin cancer*	1		✓	✓
Skin & soft-tissue Infections caused by <i>Staphylococcus aureus</i>	1		✓	
Varicella	1	✓	✓	✓
Yellow fever	1	✓	✓	✓
Zika	1		✓	
PHASE III CLINICAL TRIALS				
Chikungunya virus	1		✓	
<i>Clostridioides difficile</i> infection	1		✓	✓
COVID-19	10	✓	✓	✓
Cytomegalovirus	1		✓	
Extraintestinal pathogenic <i>Escherichia coli</i> (ExPEC)	1			✓
Human immunodeficiency virus (HIV)	1		✓	
Influenza	2		✓	✓
Lyme disease	1	✓	✓	
Meningococcal disease (A, C, W, Y and A, B, C, W, Y)	3	✓	✓	
Pneumococcal disease	1	✓		
Rabies	1	✓	✓	✓
Respiratory Syncytial Virus	6		✓**	✓
UNDER REVIEW BY THE REGULATORY AUTHORITY				
COVID-19	8	✓	✓	✓
Dengue fever	1	✓	✓	
Ebola	1	✓	✓	
Meningococcal disease (A, C, W, Y)	1	✓		

* Therapeutic vaccine

** Vaccine dedicated to maternal immunisation

Glossary

Most of the vaccine candidates in the pipelines of Vaccine Europe members address more than one challenge. This glossary represents an overview of the issues that could be potentially addressed by the candidates, grouped based on the disease they are targeting. In the classification below we divided the vaccine candidates based on their potential future use for routine immunisation (those vaccines intended for everyone in a specific country, depending on their age, medical and vaccination history) or as travel vaccination.

Legend:

AMR	Antimicrobial resistance
CR	Cancer vaccines
CC	Climate change
MI	Maternal immunisation
RI	Routine immunisation (including travel vaccines that could be used routinely in endemic countries)
ThV	Therapeutic vaccines
TrV	Travel vaccines
UPHN	Unmet public health needs (diseases for which there was no vaccine on the market by the end of July 2022)
ZOO	Zoonoses

Chikungunya virus (2) CC TrV UPHN ZOO

Clostridioides difficile infection (3) AMR RI UPHN

Coronaviruses (30) AMR RI ZOO

Cytomegalovirus (4) RI UPHN

Dengue (1) AMR CC RI TrV ZOO

Ebola (2) TrV ZOO

Epstein-Barr virus (1) CR RI UPHN

Extraintestinal pathogenic *Escherichia coli* (ExPEC) (1) AMR UPHN

Glioblastoma (1) CR ThV

Group B *Streptococcus* infection (1) MI RI UPHN

Hepatitis B* (2) CR ThV

Herpes simplex virus (1)	ThV	UPHN		
Human immunodeficiency virus (HIV) (3)	RI	UPHN		
Human metapneumovirus and parainfluenza virus 3 (hMPV/PIV3) (1)	AMR	RI	UPHN	
Influenza (9)	AMR	RI	ZOO	
Klebsiella pneumoniae (1)	AMR	RI	UPHN	
Lung/colorectal/pancreatic cancer (1)	CR	ThV		
Lyme disease (1)	RI	UPHN	ZOO	
Malaria (2)	CC	RI	TrV	ZOO
Meningococcal disease (6)	RI	TrV	UPHN	
Nipah virus (1)	RI	UPHN		
Pneumococcal disease (5)	AMR	RI		
Rabies (2)	AMR	TrV	ZOO	
Respiratory Syncytial Virus (RSV) (10)	AMR	MI	RI	UPHN
Shigellosis (1)	AMR	RI	UPHN	
Skin cancer (1)	CR	ThV		
Skin & soft-tissue Infections caused by staphylococcus aureus (1)	AMR	RI	UPHN	
Solid tumour (2)	CR	ThV		
Varicella (1)	AMR	RI		
Yellow fever (1)	RI	TrV	ZOO	
Zika (3)	CC	TrV	UPHN	

* Vaccines against Hepatitis B are also intended for routine immunisation. However, the two candidates currently present in the pipeline are designed as therapeutic agents.

References

All links were accessed in November 2022

- 1 Decouttere, C., De Boeck, K. *et al.* Advancing sustainable development goals through immunization: a literature review. *Global Health* (2021); 17, 95 <https://doi.org/10.1186/s12992-021-00745-w>
- 2 Watson, Oliver J., Barnsley, G. *et al.* Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis.* (2022); 22: 1293–302. [https://doi.org/10.1016/S1473-3099\(22\)00320-6](https://doi.org/10.1016/S1473-3099(22)00320-6)
- 3 <https://www.worldbank.org/en/topic/health/brief/antimicrobial-resistance-amr>
- 4 <https://www.vaccineurope.eu/news/publications/amr-the-central-role-played-by-vaccines-and-immunisation>
- 5 <https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts>
- 6 <https://www.who.int/news-room/questions-and-answers/item/neglected-tropical-diseases>
- 7 <https://www.vaccineurope.eu/about-us/our-members>
- 8 <https://www.cdc.gov/cmv/overview.html>
- 9 <https://www.nationalcmv.org/overview/vaccine-development>
- 10 <https://www.nature.com/articles/s41579-021-00582-z>
- 11 <https://www.cdc.gov/epstein-barr/about-ebv.html>
- 12 Cui, X., Snapper, CM. Epstein Barr Virus: Development of Vaccines and Immune Cell Therapy for EBV-Associated Diseases. *Front. Immunol.* (2021); 12:734471. <https://doi.org/10.3389/fimmu.2021.734471>
- 13 <https://www.who.int/news-room/fact-sheets/detail/hiv-aids>
- 14 <https://www.cdc.gov/surveillance/nrevss/hmpv/clinical.html>
- 15 <https://www.cdc.gov/parainfluenza/about/index.html>
- 16 Elboukari, H., Muddasir A. Parainfluenza Virus. In: *StatPearls* [Internet] (2022 Jul). Treasure Island (FL): StatPearls Publishing; PMID: 32809554.
- 17 <https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables>
- 18 <https://www.ecdc.europa.eu/en/seasonal-influenza/facts/factsheet>
- 19 Preaud, E., Durand L. *et al.* Annual public health and economic benefits of seasonal influenza vaccination: a European estimate. *BMC Public Health* (2014 Aug); 7;14:813. <https://doi.org/10.1186/1471-2458-14-813>
- 20 Largeron, N., Levy, P. *et al.* Role of vaccination in the sustainability of healthcare systems. *J Mark Access Health Policy* (2015 Aug); vol. 3. 10.3402/jmahp.v3.27043. <https://doi.org/10.3402/jmahp.v3.27043>
- 21 <https://www.cdc.gov/groupbstrep/about/index.html>
- 22 <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccines-quality/influenza>
- 23 [https://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal))
- 24 <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/meningococcal-meningitis>
- 25 <https://www.ecdc.europa.eu/en/meningococcal-disease>
- 26 <https://www.ecdc.europa.eu/sites/default/files/documents/AER-Invasive-meningococcal-disease-2018.pdf>
- 27 <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/respiratory-syncytial-virus-disease>
- 28 Staaadegaard, L., Caini, S. *et al.* The Global Epidemiology of RSV in Community and Hospitalized Care: Findings From 15 Countries. *Open forum Infect Dis.* (2021 Mar); vol. 8, 7 ofab159. 30, <https://doi.org/10.1093/ofid/ofab159>
- 29 <https://www.nivel.nl/en/project/promise-preparing-rsv-immunisation-and-surveillance-europe>
- 30 <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/vaccine-standardization/varicella>
- 31 Daulagala, SWPL., Noordeen, F., Epidemiology and factors influencing varicella infections in tropical countries including Sri Lanka. *Virusdisease* (2018 Sep); 29(3):277–284. <https://doi.org/10.1007/s13337-018-0459-z>
- 32 <https://www.who.int/travel-advice/vaccines>
- 33 <https://www.who.int/news-room/fact-sheets/detail/chikungunya>
- 34 <https://www.ecdc.europa.eu/en/chikungunya-monthly>
- 35 Puntasecca, C.J., King CH. *et al.* Measuring the global burden of chikungunya and Zika viruses: A systematic review. *PLoS Negl Trop Dis.* (2021); 15(3):e0009055. <https://doi.org/10.1371/journal.pntd.0009055>
- 36 <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>
- 37 <https://www.ecdc.europa.eu/en/dengue-fever/facts>
- 38 <https://www.ecdc.europa.eu/sites/default/files/documents/Communicable-disease-threats-report-30-jul-2022-public.pdf>
- 39 <https://www.who.int/news-room/fact-sheets/detail/yellow-fever>
- 40 <https://www.cdc.gov/globalhealth/newsroom/topics/yellowfever/index.html>
- 41 <https://www.worldbank.org/en/topic/health/brief/antimicrobial-resistance-amr>
- 42 <https://www.who.int/publications/i/item/9789240052451>
- 43 <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>
- 44 Heymann, DL., Kiény, MP. *et al.* Adding to the mantra: vaccines prevent illness and death and preserve existing antibiotics. *Lancet Infect Dis.* (2022); 22(8):1108–1109. [https://doi.org/10.1016/S1473-3099\(22\)00374-7](https://doi.org/10.1016/S1473-3099(22)00374-7)
- 45 Klugman, KP., Black, S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proc Natl Acad Sci. U S A* (2018); 115(51):12896–12901. <https://doi.org/10.1073/pnas.1721095115>
- 46 Pawaskar, M., Fergie, J. *et al.* Impact of universal varicella vaccination on the use and cost of antibiotics and antivirals for varicella management in the United States. *PLoS ONE* (2022 Jun); 17(6), e0269916.
- 47 <https://www.nivel.nl/publicatie/influenza-vaccination-and-antimicrobial-resistance-strategic-recommendations>
- 48 Lewnard, JA., Fries, LF. *et al.* Prevention of antimicrobial prescribing among infants following maternal vaccination against respiratory syncytial virus. *Proc Natl Acad Sci. U S A* (2022 Mar); 22;119(12):e2112410119. <https://doi.org/10.1073/pnas.2112410119>. Epub 2022 Mar 14. PMID: 35286196; PMCID: PMC8944586.
- 49 Kurauchi, A., Struchiner C.J. *et al.* Modelling the effect of a dengue vaccine on reducing the evolution of resistance against antibiotic due to misuse in dengue cases. *Theor Biol Med Model* (2020 May); 17(1):7. <https://doi.org/10.1186/s12976-020-00125-8>. PMID: 32404100; PMCID: PMC7218541.

- 50 <https://www.who.int/europe/news/item/18-11-2020-preventing-the-covid-19-pandemic-from-causing-an-antibiotic-resistance-catastrophe>
- 51 <https://www.ecdc.europa.eu/en/clostridium-difficile-infections/facts>
- 52 <https://www.cdc.gov/cdiff/what-is.html>
- 53 Poolman, J.T., Michael W. Extraintestinal Pathogenic Escherichia coli, a Common Human Pathogen: Challenges for Vaccine Development and Progress in the Field. *J Infect Dis.* (2016 Jan); 213(1): 6–13. <https://doi.org/10.1093/infdis/jiv429>. Epub 2015 Sep 2. PMID: 26333944; PMCID: PMC4676548.
- 54 Duan, Y., Gao, H. et al. Antibiotic resistance and virulence of extraintestinal pathogenic Escherichia coli (ExPEC) vary according to molecular types. *Front. Microbiol.* (2020); 11:598305. <https://doi.org/10.3389/fmicb.2020.598305>
- 55 Pitout, J.D. Extraintestinal pathogenic Escherichia coli: a combination of virulence with antibiotic resistance. *Front Microbiol.* (2012 Jan); 3:9. <https://doi.org/10.3389/fmicb.2012.00009>. PMID: 22294983; PMCID: PMC3261549.
- 56 Geurtsen, J., de Been, M. et al. Genomics and pathotypes of the many faces of Escherichia coli. *FEMS Microbiol Rev.* (2022); 46(6) fuac031. <https://doi.org/10.1093/femsre/fuac031>
- 57 <https://www.cdc.gov/hai/organisms/klebsiella/klebsiella.html>
- 58 <https://www.ecdc.europa.eu/sites/default/files/documents/antimicrobial-resistance-policy-brief-2022.pdf>
- 59 <https://www.ecdc.europa.eu/en/shigellosis/facts>
- 60 <https://www.cdc.gov/shigella/index.html>
- 61 Olaniyi, R., Pozzi, C. et al. Staphylococcus aureus - Associated Skin and Soft Tissue Infections: Anatomical Localization, Epidemiology, Therapy and Potential Prophylaxis. *Curr Top Microbiol Immunol.* (2017); 409, 199–227. https://doi.org/10.1007/82_2016_32. PMID: 27744506.
- 62 Taylor TA, Unalak CG. Staphylococcus Aureus. In: *StatPearls* [Internet] (2022 Jul). Treasure Island (FL): StatPearls Publishing; 2022 Jan. PMID: 28722898.
- 63 <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/pneumococcal-disease>
- 64 <https://www.ecdc.europa.eu/en/pneumococcal-disease/facts>
- 65 <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
- 66 <https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus>
- 67 Kanukollu, VM., Patel, BC. Herpes Simplex Ophthalmicus. In: *StatPearls* [Internet] (2022 May). Treasure Island (FL): StatPearls Publishing; 2022 Jan-. PMID: 32644620.
- 68 Saxena, M., van der Burg, SH. et al. Therapeutic cancer vaccines. *Nat Rev Cancer* (2021); 21, 360–378 <https://doi.org/10.1038/s41568-021-00346-0>
- 69 Melief, C.J., van Hall, T. et al. Therapeutic cancer vaccines. *J Clin Invest.* (2015 Sep); 125(9):3401–12. <https://doi.org/10.1172/JCI80009>. Epub 2015 Jul 27. PMID: 26214521; PMCID: PMC4588240.
- 70 <https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme>
- 71 <https://www.wcrf.org/cancer-trends/>
- 72 <https://www.cancer.gov/types/skin>
- 73 <https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/>
- 74 <https://www.wcrf.org/cancer-trends/skin-cancer-statistics/>
- 75 <https://www.thermofisher.com/be/en/home/life-science/cancer-research/solid-tumor-research.html>
- 76 <https://www.worldbank.org/en/news/press-release/2021/09/13/climate-change-could-force-216-million-people-to-migrate-within-their-own-countries-by-2050>
- 77 <https://www.who.int/news-room/fact-sheets/detail/malaria>
- 78 <https://www.who.int/news-room/fact-sheets/detail/zika-virus>
- 79 <https://www.cdc.gov/zika/about/index.html>
- 80 <https://www.cdc.gov/mmwr/volumes/66/wr/mm6612a4.htm>
- 81 Carpenter, A., Waltenburg, MA. et al. Vaccine Preventable Zoonotic Diseases: Challenges and Opportunities for Public Health Progress. *Vaccines* (2022 Jun), 10(7):993. <https://doi.org/10.3390/vaccines10070993>. PMID: 35891157; PMCID: PMC9319643.
- 82 <https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-eueea-one-health-response>
- 83 <https://www.ecdc.europa.eu/en/covid-19/latest-evidence/coronaviruses>
- 84 <https://www.ecdc.europa.eu/en/publications-data/communicable-disease-threats-report-24-30-july-week-30>
- 85 <http://www.emro.who.int/health-topics/mers-cov/mers-outbreaks.html>
- 86 <https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease>
- 87 <https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/ebola-virus-disease/facts/factsheet-about-ebola-virus>
- 88 <https://www.ecdc.europa.eu/en/borreliosis>
- 89 Marques, AR., Strle, F. et al. Comparison of Lyme Disease in the United States and Europe. *Emerg Infect Dis.* (2021 Aug) 27(8):2017–2024. <https://doi.org/10.3201/eid2708.204763>. PMID: 34286689; PMCID: PMC8314816.
- 90 <https://www.who.int/news-room/fact-sheets/detail/nipah-virus>
- 91 Singh, RK., Chakraborty, S. et al. Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies – a comprehensive review. *Vet Q.* (2019 Dec); 39(1):26–55. <https://doi.org/10.1080/01652176.2019.1580827>. PMID: 31006350; PMCID: PMC6830995. doi:10.1080/01652176.2019.1580827
- 92 <https://www.who.int/news-room/fact-sheets/detail/rabies>
- 93 <https://www.ecdc.europa.eu/en/rabies>