VACCINES BEAT

THE HOTEZ TIMES IN PUBLIC HEALTH

A candid interview with Prof. Peter Hotez

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"IMMUNIZATION IS A GLOBAL HEALTH AND DEVELOPMENT SUCCESS STORY SAVING MILLIONS OF LIVES EVERY YEAR"

WORLD HEALTH ORGANIZATION

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A candid interview with Prof. Peter Hotez

Peter J. Hotez, M.D., Ph.D. is Dean of the National School of Tropical Medicine and Professor of Pediatrics and Molecular Virology & Microbiology at Baylor College of Medicine where he is also the Co-director of the Texas Children's Center for Vaccine Development (CVD) and Texas Children's Hospital Endowed Chair of Tropical Pediatrics. He is also University Professor at Baylor University, Fellow in Disease and Poverty at the James A Baker III Institute for Public Policy, Senior Fellow at the Scowcroft Institute of International Affairs at Texas A&M University, Faculty Fellow with the Hagler Institute for Advanced Studies at Texas A&M University, and Health Policy Scholar in the Baylor Center for Medical Ethics and Health Policy. He also holds honorary DSc doctoral degrees from the Elmezzi Graduate School of Molecular Medicine (Northwell Health), Roanoke College, honorary doctoral degrees in both science and humanities by The National Autonomous University of Honduras (UNAH), and City University of New York (CUNY) Graduate School of Public Health and Health Policy.

Full Bio

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LETTER FROM EDITORS

Dear colleagues,

Welcome to the inaugural issue of Vaccines Beat, your go-to source for all updates in vaccinology!

Our aim is to provide an innovative and comprehensive global perspective on vaccines, vaccination, vaccine introduction to NIPs; by delivering monthly updates on the latest news, alerts, and scientific publications from recognized & valuable sources.

In this debut issue, we're delighted to feature Prof. Peter Hotez, who shares his insights on combating anti-science and anti-vaccine movements, addressing global inequities in vaccine research and development, and the importance of pandemic preparedness.

Our "Editors Corner" spotlights the success story of the first FDA and EMA-approved Chikungunya vaccine ever, examining its global implementation amidst the spread of Aedes mosquitoes due to climate change.

In our "Best Practice" section, we delve into the rationale behind the World Health Organization's recommendation for a single dose of the Human Papilloma Virus (HPV) vaccine, underscoring its vital role in reducing cervical cancer incidence, particularly in developing nations.

In addition to these features, we bring you the latest news & alerts, scientific publications, and official updates on ongoing clinical trials in the field of vaccines.

We're truly optimistic that this inaugural issue will capture your interest and inspire you to join our community as we embark on this exciting journey together.

Warm regards,

Javier Casellas, M.D., Ph.D.

Chief Editor

Enrique Chacon-Cruz, M.D., MSc

Chief Editor

Javier Casellas

Well-recognized Argentinian Pediatrician and Infectious Diseases Specialist with more than 17 years of experience on Medical Affairs & Clinical Research on Vaccines field within different multinatinational & recognized Pharmaceutical Companies. (GSK and Novartis Vaccines)

From 2005 to 2015 Dr. Casellas worked as Vaccines Medical Affairs / Clinical Research Director (GSK and Novartis vaccines in Latam Region) with experience on vaccine clinical research, medical affairs activities, vaccine pharmacovigilance, public & private vaccine market access, strong relationship with MoHs across Latam and supranational organizations (such as PAHO, and Sabin Institute), and has published several scientific papers and posters in international journals and meetings, among the most relevant medical activities.

Since 2016 Dr. Casellas became an Independent Vaccine Consultant. From 2016 to 2018, Dr. Casellas joined an NPO (FIDEC, Miami, FL, USA) as Medical Manager working on vaccine clinical trials along with Bill and Melinda Gates Foundation. Currently, Dr. Casellas works on global & regional Vaccine and Infectious Diseases (IDs) trials at IQVIA as Global Medical Director within the Infectious Diseases and Vaccines Team.

Enrique Chacon Cruz

Enrique Chacon-Cruz, M.D., MSc, Mexican-born medical doctor with a degree from Guadalajara, Mexico, and further specializations in Pediatrics and Infectious Diseases from institutions in Mexico City and the USA (Eastern Virginia Medical School). He also holds a Master's degree in Vaccinology and Drug Development from the University of Siena, Italy.

He is an Overseas Fellow of the Royal Society of Medicine of the United Kingdom and a member of several international associations in Infectious Diseases. Currently, he is the CEO and Founder of "Think Vaccines" (Research, Education, and Consultancy for Vaccines and Vaccinology) based in Houston, Texas.

With over 140 research items published and/or presented at international meetings and more than 500 international lectures, all focused on vaccines, vaccination, clinical trials, and vaccine-preventable diseases. The latter conducted independently or in association with the Centers for Disease Control and Prevention (CDC), the University of California in San Diego, Eastern Virginia Medical School, and several other institutions.

Additionally, he is a member of the Mexican Committee for the Elimination of Measles, Rubella, and Congenital Rubella, and the Scientific Committee on Health Issues of the Mexican Government in Baja-California. He is also the former Director of the Mexican Active Surveillance Network for Bacterial Meningitis and the former Head of the Pediatric Infectious Diseases Department and the Research Department at the General Hospital of Tijuana, Baja-California, Mexico.

Coffee with the Expert

THE HOTEZ TIMES IN PUBLIC HEALTH

A candid interview with Prof. Peter Hotez

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Felicitas Colombo, MPA

Summer hit the United States Congress and it's inferno hot in public health. Coincidentally, we had the privilege to have a candid conversation with Prof. Peter Hotez, M.D., Ph.D., a pediatrician-scientist and Dean of the National School of Tropical Medicine and Professor of Pediatrics and Molecular Virology & Microbiology at Baylor College of Medicine and Co-director of the Texas Children's Hospital Center for Vaccine Development, who shared his perspectives on many important health issues.

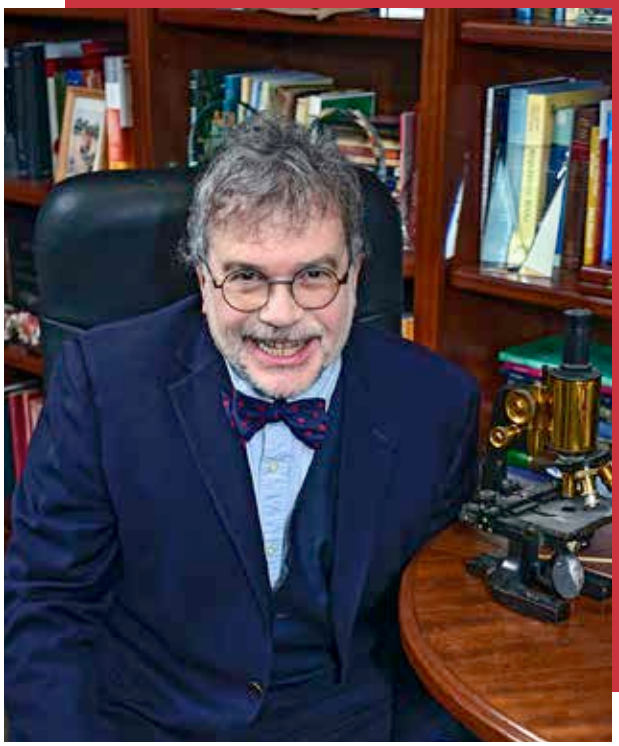
Prof. Hotez is deeply immersed in the intersection of science, politics, and public health, particularly in the realm of vaccine development and defense against anti-science movements. His career and advocacy highlight several critical themes and challenges facing global health and science policy today.

Partisan Science & Polarization

Science and politics are extremely complex ecosystems. An intricate spiderweb of actors and players that influence health policy with multidimensional repercussions. Trying to make sense of it is as difficult as making vaccines. Physicians and scientists struggle to discuss the attacks on biomedicine because they are trained not to talk about politics.

Prof. Hotez notes that attacks on science often align along partisan lines, impacting health policy decisions and public trust in scientific consensus. This polarization complicates efforts to combat diseases and promote evidence-based policies.

"All our training says we're not supposed to talk about Republicans and Democrats and liberals or conservatives or red states and blue states, but clearly the attacks are along a partisan divide, both against biomedicine and climate science. So, the fact that it now reaches the highest level of the United States Congress, that's a big concern," expressed Prof. Hotez, author of *The Deadly Rise of Anti-Science*.



Prof. Peter J. Hotez

An internationally recognized physician-scientist in neglected tropical diseases and vaccine development also a stalwart voice at the helm of the difficult journey to protect science, Prof. Hotez has received several attacks throughout his career, which spans over four decades. Keen to see more government protections to scientists from the White House Office of Science & Technology Policy and scientific societies, among other institutions, he finds solace in his work and achievements.

"I mean, I'm often asked, well, why aren't you suing all these people for defamation? And I say, yeah, I could, or I could make vaccines to save the world," shared Prof. Hotez during our conversation.

Science above all

As both a vaccine scientist and autism parent, Prof. Hotez began his journey to defend vaccines more than two decades ago and now serves as

a passionate advocate against the growing 'antivax' activism. Becoming these groups' target gave him ample visibility to contest the dangerous and pervasive anti-vaccine rhetoric.

"So, my life has had this duality ever since. The best of science, trying to make good, safe and effective vaccines for global health; but also countering the anti-vaccine activism. And in some ways, that may be just as important as making vaccines," explained Prof. Hotez.

The world is currently experiencing strong pushbacks against vaccine mandates through aggressive anti-vaccine activists that discredit the effectiveness and safety of vaccination. In the zeal to push back against mandates, they're also weaponizing the health and science communication. Prof. Hotez is concerned this could be reversing all the gains of the last 20 years through the Gavi Alliance and latest World Health Organization (WHO) data confirms that childhood immunization rates have stalled.

"So, we peaked at around 2019, 2020, with 86% of the world's kids being vaccinated, and now it's slowly going down again. And yet not a big decline, but it's the first time it's gone the wrong direction in 20 years," said Prof. Hotez.

With so much information available, combating disinformation is not an easy task. Improving science communications is key to successful health policy. Protecting scientists, Prof. Hotez claims, is at the center of this conflict because the attacks are not only against science but also portraying scientists as public enemies or enemies of the state.

"Even worse, sometimes it's the silence of the friends is almost as bad as the words of the enemy," he concluded.

Yet, as he openly explains, there are many factors driving the emergence of diseases, and anti-science forces are only one of them. Others include climate change, urbanization and poverty.

The Next Pandemic

Scientists are seeing a cadence of regular pandemics. Whether it's SARS and MERS, COVID and Ebola, H1N1, or H5N1 currently and hopefully not accelerating, Prof. Hotez believes we are at high risk for a major zoonotic flu pandemic, either from pigs or from birds.

"I think we have to work on that premise that, eventually, there will be a major zoonotic and catastrophic flu pandemic. And what are we doing in terms of surveillance? And the answer is we're not doing much," he sustains.

What he is referring to is the Center for Disease Control's (CDC) One Health surveillance program. A collaborative, multisectoral, and transdisciplinary approach working at different government levels with the goal of achieving optimal health outcomes through monitoring and controlling public health threats. Through the collaboration of all relevant disciplines and sectors, it aims to learn about how diseases spread among people, animals, plants, and the environment.

"I think we're just not prepared yet to really take that on, and that's got to be a priority. One of the things that COVID taught us was, yes, there was a public health impact, but it was so much more than that, right? It affected the global economy and global security, and it will happen again with the zoonotic flu. And so, we've got to get out of this mindset of doing everything on the cheap," explains Prof. Hotez, who highlights that the need for surveillance efforts in areas of biodiversity extends throughout the world, especially in low- and middle-income countries.

During the COVID-19 pandemic, mRNA, particle and adenovirus vaccines were developed quickly. The issue when relying on a brand-new technology, is that there is a learning curve before going from zero to the 15 billion doses needed to vaccinate the world. These initial doses quickly were bought up by the U.S., Canada and Western European countries, leaving the low- and middle-income countries vulnerable.

"The question is how do you do this in an equitable form? How do you also encourage technologies that could be scaled up locally by vaccine producers in low- and middle-income countries?" questions Prof. Hotez, who was nominated for the Nobel Peace Prize for his work to develop and distribute a low cost (recombinant protein) COVID vaccine for the developing world by transferring previously researched technology with no patent, minimizing strings attached to vaccine producers.

Through this initiative, by 2022, 100 million people got vaccinated in India and Indonesia. A testimony that not only big pharma can do big things. Nevertheless, vaccines for low- and middle-income

countries doesn't seem to be anybody's priority.

"For each vaccine we must go begging for support. That becomes a full-time job for me, trying to raise funds for each vaccine. It's exhausting and it's a lot of work and very inefficient. So, it would be nice if we had a steadier stream of funding support," expressed Prof. Hotez.

"How do we get better buy-in from all the G20 countries to contribute funds for vaccines and recognize that, again, these pandemics and these neglected diseases are more than just health threats, they're economic and global security threats and treat them seriously," he continued.

Pre-qualification mechanisms at WHO are still putting a velvet rope around big pharma, making their path much more straightforward and easier. A procedure Prof. Hotez is confident WHO is committed to fixing.

Currently, to get rapid approval and dissemination of a vaccine, you either have to go through the WHO's pre-qualification mechanism or one of the so-called 'stringent regulatory authorities', and then it gets concurrence by WHO. One way Prof. Hotez believes getting the world vaccinated could move a lot faster would be to provide the biggest producers of vaccines in the world, such as India, Indonesia or Brazil, 'stringent regulatory' status.

"Our technical ability to make vaccines has outpaced the political, social and financial instruments that we have to ensure their equitable distribution. So that turns out to be as complicated as the science itself," vehemently expressed Prof. Hotez.

The challenges & opportunities ahead

"Preventing the Next Pandemic", a book Prof. Hotez wrote in 2021, looks at how all these forces are converging. He explains it is this constellation of 21st century forces, of which climate change is a big aspect because so many of these viruses derive from bats, and bats are migrating in different patterns in search of new habitats and food sources because of climate change. Deforestation, urbanization, in addition to political instability and anti-science are indeed important as well.

The convergence of these and other forces is contributing to these illnesses appearing at an alarming rate. Not only are we seeing an increased frequency in the cadence of pandemic threats such as Ebola and Coronavirus infections, as well as zoonotic influenzas, but there's also a notable increase in neglected tropical diseases, including places where we haven't seen them before. Hence, it's not only the pandemic threats, but also parasitic and neglected tropical diseases, which include arbovirus infections (dengue, Zika, chikungunya, and yellow fever) tick-borne illnesses, and parasitic infections (Chagas disease and hookworm anemia).

Technology is advancing at an exceedingly fast rate and there currently are many options for new vaccine technologies, whether it's mRNA, particle vaccines, or traditional yeast-based recombinant protein vaccines. Prof. Hotez believes another challenge is going to be to discern what the best technology will be for any given vaccine.

"And then realizing that making the vaccine may not be the hardest part anymore because you've got to, one, get people to accept new vaccines," continued Prof. Hotez.

He worries that the recent vaccine refusal, or fatigue, is going to extend to other new vaccines being introduced. The question is, what is the upper limit of new vaccines people will accept and how to bring them into the system in combination, as a way to streamline the process so it fits into the health system.

"I think my big worry is that we are seeing, whatever metaphor you want to use, a tear in the matrix or some gaps now on our global vaccination ecosystem," concluded Prof. Hotez.

Looking ahead, Prof. Hotez calls for sustained global cooperation and financial commitments to address neglected tropical diseases, pandemic threats, and broader health challenges. He emphasizes the critical need to acknowledge the risks posed by politically motivated anti-vaccine and anti-science movements, which are increasingly spreading beyond the United States to become global issues. He continues to emphasize the importance of scientific integrity, public engagement, and equitable health policies.

In summary, Prof. Hotez's work and advocacy underscore the complexities of navigating science within political landscapes, the imperative of global health equity, and the urgency of preparing for future pandemics. His insights and initiatives highlight the ongoing need for collaborative efforts and innovative solutions to safeguard public health on a global scale.

News & Alerts

MOST RELEVANT MONTHLY NEWS ON VACCINATION AND EMERGING DISEASES WITH BIBLIOGRAPHIC ALERTS

A summary of the latest News & Alerts in the fields of vaccinology, vaccines, vaccination, and vaccine-preventable diseases. We curate the latest information on regulatory updates, emerging trends, breakthroughs in vaccine technology, vaccine safety and efficacy, global immunization developments and outbreak alerts, as a resource to keep our community informed.

NIH-sponsored trial of nasal COVID-19 vaccine opens

Candidate vaccine could provide enhanced breadth of protection against emerging SARS-CoV-2 variants.

Published: Julio 1, 2024.

https://www.nih.gov/news-events/news-releases/nih-sponsored-trial-nasal-covid-19-vaccine-opens#:~:text=A%20Phase%201%20trial%20testing,sites%20in%20the%20United%20States.

Investigation into an outbreak of Shiga toxin-producing E. coli (STEC) O145 in Great Britain, May to June 2024

Published June 27, 2024.

https://www.gov.uk/government/publications/shiga-toxin-producing-e-coli-outbreak-0145-may-to-june-2024/investigation-into-an-outbreak-of-shiga-toxin-producing-e-coli-stec-0145-in-great-britain-may-to-june-2024

CDC A(H5N1) Bird Flu Response

Update June 28, 2024

https://www.cdc.gov/bird-flu/spotlights/h5n1-response-06282024.html

Multi-country outbreak of mpox (monkeypox) – External Situation Report 34

Published 28 June 2024 (WHO)

https://reliefweb.int/report/world/multi-country-outbreak-mpox-monkeypox-external-situation-report-34-published-28-june-2024

Oropouche Fever in the Americas

Published June 27, 2024.

https://wwwnc.cdc.gov/travel/notices/level1/oropouche-fever-brazil

Global Dengue

Published June 25, 2024.

https://wwwnc.cdc.gov/travel/notices/level1/dengue-global

Multi-country outbreak of cholera, External situation report #15 – 19 June 2024 (WHO)
Published June 19, 2024.

https://www.who.int/publications/m/item/multi-country-outbreak-of-cholera-external-situation-report-15—19-june-2024.

U.S. FDA Approves CAPVAXIVE™ (Pneumococcal 21-valent Conjugate Vaccine) for Prevention of Invasive Pneumococcal Disease and Pneumococcal Pneumonia in Adults
Published June 17, 2024

https://www.fda.gov/vaccines-blood-biologics/capvaxive

COVID-19 epidemiological
Update 17 June 2024 (WHO)

https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-168

Human infections caused by Avian Influenza A(H5N2) – Mexico (WHO).
Published June 14, 2024.

https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON524

WHO South-East Asia Region Epidemiological Bulletin, 13th edition (2024), 26 June 2024. Reporting period: 10 – 23 June 2024
https://reliefweb.int/report/bangladesh/who-south-east-asia-region-epidemiological-bulletin-13th-edition-2024-26-june-2024-reporting-period-10-23-june-2024

Epidemic and emerging disease alerts in the Pacific as of 04 June 2024
https://reliefweb.int/map/world/epidemic-and-emerging-disease-alerts-pacific-04-june-2024

Epidemiological Alerts and Updates (PAHO)
Up to June 2024.

https://www.paho.org/en/epidemiological-alerts-and-updates

Africa CDC Weekly Event Based Surveillance Report, June 2024
https://africacdc.org/download/africa-cdc-weekly-event-based-surveillance-report-june-2024/

Global Measles
Published May 28, 2024.

https://wwwnc.cdc.gov/travel/notices/level1/measles-globe

Latest Relevant Publications

LATEST PUBLISHED PAPERS AND COMMENTARIES FROM THE CHIEF EDITORS

Latest impactful scientific publications that stand out for their potential bearing on healthcare. We introduce groundbreaking research findings, innovative treatment modalities, results from phase 1 to 3 vaccine clinical trials, or paradigm-shifting discoveries that redefine our understanding of infectious diseases and therapeutic approaches for all vaccine-preventable diseases.

01

"Impact of interventions to improve HPV vaccination acceptance and uptake in school-based programs: Findings of a pilot project in Quebec".
PUBLISHED: Vaccine. July 11, 2024. https://doi.org/10.1016/j.vaccine.2024.04.089

Editorial comment: A multicomponent strategy to improve HPV vaccination among children in schools from Quebec.

02

"Accelerating Global Measles and Rubella Eradication—Saving Millions of Lives, Preventing Disability, and Averting the Next Pandemic".
PUBLISHED: Vaccines. June 20, 2024. https://doi.org/10.3390/vaccines12060699

Editorial comment: In response to the rising number of measles cases and outbreaks globally, there is a need to accelerate immunization programs and implement additional epidemiological measures.

03

"COVID-19 Booster Vaccination Status and Long COVID in the United States: A Nationally Representative Cross-Sectional Study".
PUBLISHED: Vaccines. June 20, 2024. https://doi.org/10.3390/vaccines12060688

Editorial comment: Few studies have explored the association of booster doses on severe disease outcomes and long COVID. This cross-sectional analysis used data from the 2022 US National Health Interview Survey data to investigate how vaccination status correlates with COVID-19 infection severity and long COVID among previously infected individuals. Their results showed that by having at least one booster there was a reduction in long COVID odds by 24% (aOR = 0.76, p = 0.003), however, completing only the primary vaccine series did not significantly decrease the likelihood of severe illness or long COVID. These findings support the continued promotion of booster vaccinations to mitigate long COVID risks in vulnerable populations.

04

"Filling two needs with one deed: a combinatory mucosal vaccine against influenza A virus and respiratory syncytial virus".
PUBLISHED: Front Immunol. June 20, 2024. https://doi.org/10.3389/fimmu.2024.1376395

Editorial comment: Early pre-clinical but promising results of a combined Influenza and RSV mucosal vaccine in mice.

05

"The role of vaccines in reducing antimicrobial resistance: A review of potential impact of vaccines on AMR and insights across 16 vaccines and pathogens".
PUBLISHED: Vaccine. June 13, 2024. https://doi.org/10.1016/j.vaccine.2024.06.017

Editorial comment: An insightful review on how vaccination significantly reduces antimicrobial resistance, highlighting it as an essential tool in combating this global and deeply concerning issue.

06

"The macroeconomic impact of a dengue outbreak: case studies from Thailand and Brazil."
PUBLISHED: PLOS NTDs. June 3, 2024. https://doi.org/10.1371/journal.pntd.0012201

Editorial comment: A compelling model that quantifies economic losses due to dengue outbreaks considers not only direct and indirect costs but also the financial impact of reduced tourism, expressed in billions of US dollars.

07

"Optimisation of dose level and vaccination schedule for the VLA15 Lyme borreliosis vaccine candidate among healthy adults: two randomised, observer-blind, placebo-controlled, multicentre, phase 2 studies".
PUBLISHED: Lancet Infect Dis. May 31, 2024, with corrections on June 14, 2024. https://doi.org/10.1016/S1473-3099(24)00175-0.

Editorial comment: Lyme disease vaccine promising initial results from a Phase 2 clinical trial

08

"Epitopes in the HA and NA of H5 and H7 avian influenza viruses that are important for antigenic drift".
PUBLISHED: FEMS Microbiology Reviews, May 11, 2024. https://doi.org/10.1093/femsre/fuae014

Editorial Comment: Analyses included 32 PCV13 sites (488,758 cases) and 15 PCV10 sites (46,386 cases) in 30 countries, primarily high-income (39 sites) using booster dose schedules (41 sites). By six years postPCV10/13 introduction, IPD due to PCV10-type serotypes and PCV10-related serotype (ST)6A declined substantially for both products (children aged <5 years: 83–99% decline; adults aged ≥65 years: 54–96%).

Introduction of PCV10/13 substantially and rapidly reduced IPD in young children and more moderately in older ages. Non-vaccine-type serotypes increased approximately 2–3-fold by six years post-PCV10/13 introduction. Sustained increases in ST19A at PCV10 sites and declines at PCV13 sites compared to pre-PCV suggest that PCV13 provides greater net impact than PCV10.

09

"Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalization for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study".

PUBLISHED: Lancet Infect Dis. April 30, 2024. https://doi.org/10.1016/S1473-3099(24)00215-9

Editorial comment: Early data showing significant effectiveness of Nirsevimab in infants substantially reducing infant hospitalizations for RSV-associated LRTI, severe RSV-associated LRTI requiring oxygen, and all-cause LRTI when given in real-world conditions. These findings offer policy makers and health authorities robust, real-world, population-based evidence to guide the development of strategies for RSV prevention.

10

"Realizing the potential of correlates of protection for vaccine development, licensure and use: short summary".

PUBLISHED: npj Vaccines. April 29, 2024. https://doi.org/10.1038/s41541-024-00872-6

Editorial comment: Licensing is a key step on the pathway to vaccine utilization but not the final one. The decision to use a new vaccine product will be made by ministry of health policymakers, generally having sought a recommendation from independent advisory committees such as national immunization technical advisory groups (NITAGs). In turn, NITAGs are influenced by the recommendations made by global bodies such as the Strategic Advisory Group of Experts on Immunization (SAGE) and regional immunization technical advisory committees (RITAGs).

In some cases, efficacy data may be available from similar populations to inform policymaking. If they are not, CoP could provide a tool for assessing likely protection in local populations if the strength and reliability of the association between CoP and efficacy within the population of interest is well established.

11

"COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals".

PUBLISHED: Vaccine. April 2, 2024. https://doi.org/10.1016/j.vaccine.2024.01.100

Editorial comment: The largest study (99 million subjects) by The Global COVID Vaccine Safety (GCoVS) Project comparing adverse event of special interest (AESI) occurring up to 42 days following vaccination with mRNA (BNT162b2 and mRNA-1273) and adenovirus-vector (ChAdOx1) vaccines.

12

"Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomized phase 3 trial".

PUBLISHED: Lancet. February 10, 2024. https://doi.org/10.1016/S0140-6736(23)02511-4

Editorial comment: Very encouraging results of a second efficacious and safe malaria vaccine, which, alongside the RTS,S vaccine, will bolster efforts in the ongoing fight against this deadly disease, especially in Africa.

Editors Corner

VACCINE AGAINST CHIKUNGUNYA: GOOD NEWS, A VACCINE HAS BEEN APROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA) AND THE EUROPEAN MEDICINES AGENCY (EMA)

The importance of immunobridging,
and future potential strategies and interventions

Recently, a phase 3 clinical trial published at The Lancet showed high immunogenicity and good safety profile of a one shot of a live attenuated Chikungunya (CHIK) vaccine (1), leading to further look for further approval of a CHIK vaccine first time in history.

CHIK is s a mosquito-borne viral disease caused by the Chikungunya virus (CHIKV), an RNA virus in the alphavirus genus of the family Togaviridae. The name Chikungunya derives from a word in the Kimakonde language, meaning "to become contorted". It is transmitted by mosquitoes, most commonly Aedes aegypti and Aedes albopictus, which can also transmit Dengue and Zika viruses. These mosquitoes bite primarily during daylight hours. They lay eggs in containers with standing water. Both species feed outdoors, and Ae. aegypti also feeds indoors (2,3).

When an uninfected mosquito feeds on a person who has CHIKV circulating in their blood, the mosquito can ingest the virus. The virus then replicates in the mosquito over several days, gets to its salivary glands, and can be transmitted into a new human host when the mosquito bites them. The virus again begins to replicate in this newly infected person and reaches high concentrations in their blood, at which point they can further infect other mosquitoes and perpetuate the transmission cycle (3).

In symptomatic patients, the incubation period of CHIKV is 4–8 days after the bite of an infected mosquito. It is characterized by an abrupt onset of fever, frequently accompanied by severe joint pain. The joint pain is often debilitating and usually lasts for a few days but may be prolonged, lasting for weeks, months or even years. Other common signs and symptoms include joint swelling, muscle pain, headache, nausea, fatigue, and rash. Since these symptoms overlap with other infections, including those with Dengue and Zika viruses, cases can be misdiagnosed. In the absence of significant joint pain, symptoms in infected individuals are usually mild and the infection may go unrecognized (3).

Most patients recover fully from the infection; however, occasional cases of eye, heart, and neurological complications have been reported with CHIKV infections. Patients at extremes of the age spectrum are at higher risk for severe disease. Newborns infected during delivery and older people with underlying medical conditions may become severely ill and CHIKV infection can increase the risk of death. Once an individual is recovered, available evidence suggests they are likely to be immune from future infections (3).

The diagnosis of CHIK is usually by RT-PCR, though serologic tests can also be performed (2,3).

From the epidemiologic perspective, CHIKV leads to over 2 million cases reported since 2005 and has particularly been identified in over 110 countries in Asia, Africa, Europe, and the Americas (2,3). Historically, CHIKV has been endemic in tropical and subtropical regions of sub-Saharan Africa and Southeast Asia, where two distinct CHIKV transmission cycles exist. CHIKV is maintained in a rural enzootic transmission cycle, which occurs between various forest or savannah Aedes mosquitoes and animal reservoirs, with nonhuman primates being the presumed major reservoir host (3). Occasional introduction of the virus into urban areas is thought to cause periodic outbreaks of CHIKV disease (3). Urban transmission is mediated primarily by Aedes aegypti or Aedes albopictus mosquitoes and occurs in a human-mosquito-human transmission cycle (3). Although is not a common lethal disease (~0.1% mortality), these outbreaks can lead to a high socioeconomic burden since, but manifestations of CHIKV infection that lead to acute and chronic disability have considerable implications, including a substantial impact on quality of life for infected patients as well as considerable economic and community consequences (3).

As with Dengue and Zika, treatment of CHIK is symptomatic, with no current available antivirals. The only preventive methods are mosquito-control activities, and no current vaccine was available, until now (2,3).

Recent CHIK outbreak in Paraguay, and the emergence of new concepts of CHIK disease: During October 1, 2022–March 11, 2023, a total of 81,037 suspected, probable, or confirmed CHIK cases was recorded by the Paraguayan Ministry of Health; among these, 75,911 (94%) occurred during 2023. Most cases occurred in the Central Department (49,070; 61%) and Asuncion (16,094; 20%). Cumulative national incidence was 1,073 cases per 100,000 population (3,088 per 100,000 population in Asuncion). Weekly case counts in Asuncion and Central Department declined slightly after epidemiologic week 6, but an increasing number and proportion of cases were subse-

Research and Development (R&D) for a CHIK vaccine has several difficulties, leading to new solutions:

1. Though endemic in many countries, the highest relevant impact of the disease is during outbreaks. The continuous threat of CHIK (re-)emergence and the huge public health and economic impact of the epidemics and outbreaks, makes the development of a safe and effective vaccine a priority.
2. In general, vaccine efficacy can be measured using three different parameters: (a) protection against local and/or systemic virus replication, (b) protection from development of clinical disease, and (c) development of an anamnestic response following challenge. For CHIK, some experts said that the lethal-arthritis (mouse) model is the most appropriate for prediction of vaccine efficacy in humans because it utilizes the extreme susceptibility of the immunodeficient mouse while allowing the simultaneous testing of the largest number of efficacy parameters, namely mortality, foot swelling, viremia, viral persistence in target organs, levels of IL-6 (and other cytokines) and ferritin. However, none of the above can contemplate feasibility, precision, and cost-effectiveness, altogether (5).
3. Hence, developing a phase 3 Clinical Trial looking for efficacy it is evidently unfeasible, since also outbreaks are unpredictable, however, in countries where Aedes is present, a persistent and latent risk, the recent experience in Paraguay evidently leads us that early intervention could it lead to a lesser extent of cases, mortality, and sequelae.
4. A "phase 3" Clinical Trial searching for a surrogate of protection is indeed the best option. Accordingly, a longitudinal cohort study performed in Cebu City, Philippines (6) found that the presence of pre-existing chikungunya virus (CHIKV) neutralizing antibodies (NAb) was associated with a decreased risk of symptomatic CHIKV infection. Among 854 participants who completed the 12-month visit (year 1) and 765 who completed the 24-month visit (year 2), 25 symptomatic CHIKV infections and 104 subclinical seroconversions occurred among 615 individuals with no detectable pre-year NAb in year 1 and 444 in year 2, while no symptomatic infections and one subclinical seroconversion occurred in those with a pre-year PRNT80 (plaque reduction neutralization test) titer ≥1:10. Pre-year PRNT80 titer ≥1:10 was associated with zero relative risk of symptomatic CHIKV infection and 0.018 risk of subclinical seroconversion in real life (6).

quently reported from outlying regions, including along borders with Brazil and Argentina (4).

Among 47,116 probable or confirmed cases, 27,147 (58%) were in females, and the median age was 36 years (range = 0 days–103 years); 4,604 (10%) hospitalizations and 52 (<1%) deaths attributable to CHIKV infection were reported. Among 208 (0.4%) cases in infants aged ≤29 days (newborns), 140 hospitalizations and eight deaths were reported, accounting for the highest case fatality rate (3.8%) among all age groups. Among fatal neonatal cases, the timing of symptom onset suggested intrapartum transmission in 75%, and mosquito borne transmission in 25%, indeed a concerning concept in CHIK transmission. Among adults aged ≥60 years, 10,617 cases and 1,878 hospitalizations (41% of all hospitalizations) were reported. Within this group, 32 deaths occurred; 23 (72%) and 13 (41%) deceases had documented cardiovascular disease and diabetes, respectively, and 20 (63%) had two or more comorbidities. The highest case fatality rate among adults aged ≥60 years occurred among those aged ≥80 years (0.6%; 11 of 1,719 cases) (4).

On June 24th, 2023, VLA1553, a live-attenuated vaccine candidate for active immunization and prevention of disease caused by CHIKV was tested in a phase 3 Clinical Trial searching for safety and immunogenicity, funded by Valneva, Coalition for Epidemic Preparedness Innovation (CEPI), and EU Horizon 2020 (1). Accordingly, 4128 participants were enrolled and randomized (3093 to VLA1553 and 1035 to placebo). 358 participants in the VLA1553 group and 133 participants in the placebo group discontinued before trial end. The per-protocol population for immunogenicity analysis comprised 362 participants (266 in the VLA1553 group and 96 in the placebo group). After a single vaccination, VLA1553 induced seroprotective CHIKV NAb levels (PRNT80 titer ≥1:10) in 263 (98·9%) of 266 participants in the VLA1553 group (95% CI 96·7–99·8; p<0·0001) 28 days post-vaccination, independent of age. VLA1553

was generally safe with an adverse event profile similar to other licensed vaccines and equally well tolerated in younger and older adults.

On June 23rd, 2023, the Advisory Committee on Immunization Practices (ACIP) of the CDC reported that in the US, a CHIKV vaccine it is indeed on the scope (7), and, considering that the Food and Drug Administration (FDA) in November 9th, 2023 has given the VLA1553 vaccine approval for preventing CHIK disease as a travelers' vaccine (8), Additionally, the European Medicines Agency (EMA) has performed a technical validation of the Marketing Authorization Application (MAA) for Valneva's single-shot CHIK vaccine candidate VLA1553 and has determined that all essential regulatory elements required for scientific assessment were included in the application. The MAA was granted accelerated assessment by EMA's Committee for Medicinal Products for Human Use (CHMP) based on the vaccine candidate's "major interest for public health and therapeutic innovation" (9). Furthermore, as of May/31st/2024, the EMA granted authorization for adults 18 years or older, becoming the first vaccine vs. CHIK ever approved in the European Union (10).

Since nor the World Health Organization (WHO) and the Pan American Health Organization (PAHO) have not yet made any recommendations on CHIK vaccination, our thoughts, despite the hurdles of developing a wide phase 3 Clinical trial, licensure of the first CHIK vaccine (VLA1553) is within reach. However, at first, it may likely only be available for use in adults (18 years or older) in relatively few high-income markets. Nevertheless, before the vaccines is licensed for use in countries where CHIKV is endemic – and where the

disease burden is greatest – is further data from extended phase 3 needed?, our guess it is not, however, phase 4 (or effectiveness) studies will be required to establish long-term safety of VLA1553, and to answer critical questions to help health authorities to plan vaccination strategies, such as: should endemic countries include potential CHIK vaccines in routine immunization programs or as an outbreak response vaccine (like in Paraguay)? What volumes of vaccine would be needed in these scenarios? How will sufficient volumes of vaccine be procured? Would the vaccine be included also in children and pregnant women?

In summary, a new milestone has been achieved, and CHIK vaccination is in an early and oncoming horizon, however, several vaccination strategies and safety issues should be performed in order to further establish solid recommendations.

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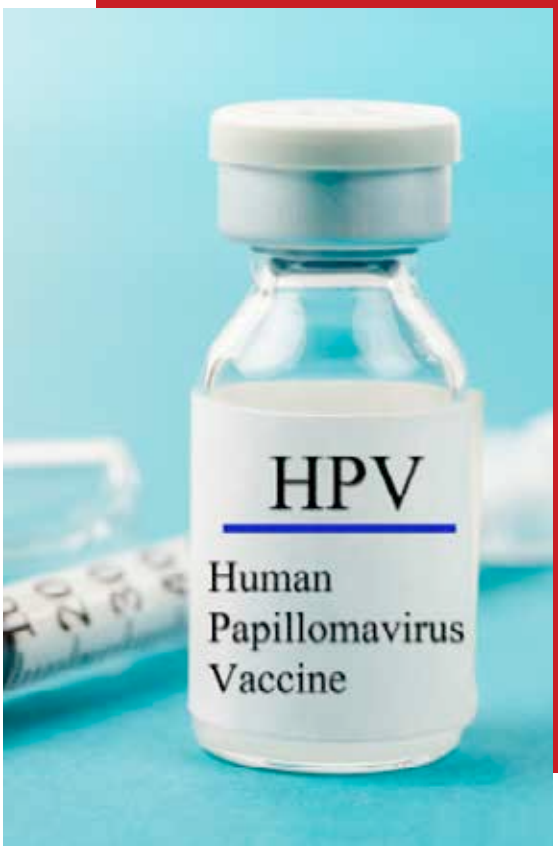
Best Practice

ONE DOSE OF HUMAN PAPILLOMA VIRUS VACCINE AS A GLOBAL STRATEGY TO PREVENT CERVICAL CANCER



Even though Human Papilloma Virus (HPV) causes cancer in several epithelia, the priority purpose of HPV massive immunization is the prevention of cervical cancer in women, which accounts for 82% of all HPV-related cancers (1). The 2020 WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem recommends that HPV vaccines should be included in all national immunization programs and should reach 90% of all girls by age 15 by 2030 (2). Prevention of cervical cancer is best achieved through the immunization of girls before they become sexually active. All currently licensed bivalent, quadrivalent and nonavalent HPV vaccines have excellent safety profiles and are highly efficacious.

The Costa Rica Vaccine Trial (CVT):

A phase III randomized clinical trial provided the initial data that one dose of the HPV vaccine could provide durable protection against HPV infection. Although the study design was to administer all participants three doses of HPV or control vaccine, 20% of women did not receive the three-dose regimens, mostly due to involuntary reasons unrelated to vaccination. Antibody levels after one dose, although lower than levels elicited by three doses, were 9-times higher than levels elicited by natural infection. Importantly, levels remained essentially constant over at least seven years, suggesting that the observed protection provided by a single dose might be durable (3).

KEN SHE 2vHPV and 9vHPV RCT:

The primary objectives of this randomized, multi-center, double-blind, controlled trial9 were to test the efficacy of immediate single dose nonavalent (9vHPV) or bivalent (2vHPV) HPV vaccination to prevent incident persistent HPV 16/18 infection. Results: At 18 months were: HPV 16/18 vaccine efficacy (VE) 97.5% (CI: 81.7-99.7%) for both 9vHPV and 2vHPV. For the sensitivity cohorts, VE against HPV16/18 9vHPV was 98.2% (CI: 86.6-99.7), 2vHPV 94.4% (CI:82.1-99.3) and extended sensitivity 100% VE (4).

India IARC 4vHPV trial:

The Working Group reviewed the latest available data from this Indian cohort study which commenced in 2009 as a cluster RCT of 2 vs 3 doses quadrivalent (4vHPV) in 10–18-year-old girls with loss of randomization due to stopping of the study in April 2010 leaving 4 groups: 3-dose, 2-dose per protocol, 2- dose default (at 0, 2 months), and single-dose default groups. Results: Immunoge-

nicity: Although the antibody titers to HPV types 16/18 induced by a single dose were inferior, a 10-year immunogenicity analysis using M9 ELISA test showed a steady plateau for HPV types 16 and 18. 95.4% of one-dose recipients were still seropositive for HPV16 as were 41.7% for HPV18. Efficacy: One-dose recipients had low rates of incident (3.1%) and persistent (0.1%) HPV 16/18 infection similar to the 2 (2.6%/0.1%) and 3 dose (2.9%/0.1%) groups. On the other hand, the unvaccinated control group (retrospectively recruited and non-randomized) had higher 16/18 infection rates (incident 9.7%, persistent 2.7%) (5).

DoRIS trial - Dose Reduction Immunobridging and Safety Study of 9vHPV and 2vHPV in Tanzanian girls:

The study included 930 girls 9-14 years in 6 arms (155 in each arm) and is the first trial of one dose in the target age group. Results: The study found that 1 dose was non-inferior to 2 or 3 doses for HPV16 seropositivity at month 24 for both 2vHPV and 9vHPV. For HPV18, the non-inferiority criterion was met for 2vHPV but not for 9vHPV (6).

WHO-Summary of findings 1 vs 2 or 3 HPV vaccine doses:

With the above data, in addition to a systematic review (7), the key findings were that, whilst the immunogenicity of 2 or 3 doses is superior to one, high seropositivity is observed after one dose with all vaccines. The efficacy of two doses is not clearly superior to 1 and there was no difference in efficacy of 3 compared to 1 dose against 16/18 HPV infection (or cross protection against infection with 31/33/45) from the Costa Rica or India studies. More variation was seen in observational studies. Immunogenicity. There was high certainty evidence that one dose of HPV vaccine resulted in lower Geometric Mean Titers (GMTs) for HPV 16 and 18 than two or three doses and this was sustained for up to 5 years. There was high certainty evidence that one, two or three doses of HPV vaccine resulted in similarly high rates of seropositivity to HPV 16 and 18 and this was sustained for up to 11 years. HPV infections. There was low certainty evidence that one dose of HPV vaccine resulted in little to no difference in persistent HPV 16/18 infections compared with two or three doses (2).

WHO-Recommendations for HPV vaccination to prevent cervical cancer:

Current evidence suggests that a single dose has comparable efficacy and duration of protection as a 2-dose schedule and may offer program advantages, be more efficient and affordable. The large majority of cervical cancer cases in 2020 (88%) occurred in low-middle income countries, where they account for 17% of all cancers in women, compared with only 2% in high-income countries. In addition, one dose will contribute to improved coverage. From a public health perspective, the use of a single dose schedule can offer substantial benefits that outweigh the potential risk of a lower level of protection if efficacy wanes over time, although there is no current evidence of this (2).

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Latest Clinical Trial Reviews

HOW NEW VACCINES ARE DEVELOPED

The U.S. Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccine use in the United States.

The general stages of vaccine development are:

- Research and Discovery
- Proof of Concept
- Testing the Vaccine
- The Manufacturing Process
- Approving the Vaccine
- Recommending the Vaccine for Use
- Monitoring Safety After Approval
- Research and Discovery

In this early stage of vaccine development, researchers explore their idea for a potential vaccine. Vaccine development often takes 10-15 years of laboratory research, usually at a company in private industry, but often involves collaboration with researchers at a university.

Proof of Concept

Before a vaccine can be tested in people, researchers study its ability to cause an immune response with small animals, like mice.

At this stage, researchers may make adjustments to the vaccine to make it more effective. Vaccine effectiveness is important because it measures how well vaccination protects people against outcomes such as infection, symptomatic illness, hospitalization, and death.

If the vaccine shows promising enough results, it moves forward to clinical trials for testing in people.

Testing the Vaccine

Next, the vaccine enters a clinical development stage, which is also called a clinical trial. To do this, researchers submit an Investigational New Drug (IND) application to FDA, which includes data from animal studies, information on manufacturing technology, and the quality of the vaccine. Vaccine quality is important because it affects how well it will work to provide long- and short-term protection against disease. The clinical development stage is a three-phase process, which may include a fourth phase if the vaccine is approved by FDA.

The following is one of the sources where ongoing clinical trials on vaccines can be found: https://clinicaltrials.gov/search?cond=Vaccines

Guest Contributors

THE POTENTIAL FOR A NEW LYME DISEASE VACCINE

Growing need for proactive measures

Lyme disease, caused by Borrelia burgdorferi transmitted through infected Ixodes ticks, is the most prevalent vector-borne infectious disease in the Northern hemisphere (1), often leading to long-lasting consequences. The United States has only 63,000 reported cases of Lyme disease, even though recent data estimates 476,000 people may be diagnosed and treated annually (2), while 65,500–85,000 (3) cases are reported annually with an estimated 200,000 diagnosed and treated in Europe (4). Consequently, the actual cases are often overlooked or misinterpreted and vastly underreported.

Early symptoms such as erythema migrans (5), a bullseye-shaped rash, or nonspecific symptoms like fatigue, fever, and headache can be easily missed. If untreated, Lyme disease can progress to serious complications affecting the skin, joints, heart, or nervous system. Unfortunately, the disease's high prevalence persists despite increasing awareness, particularly in areas where it is endemic and up to half of surveyed ticks can carry Borrelia bacteria.

Preventative measures such as insect repellents and checking for ticks are recommended but have limited impact on reducing Lyme disease cases. Research published in BMC Infectious Diseases shows that a single dose of antibiotics, if administered early, decreased the likelihood of developing Lyme disease following a tick bite compared to placebo (1). However, early intervention is crucial as, if left untreated because of a missed diagnosis, chronic outcomes can develop, which are unresponsive to typical Lyme disease treatment. The increase in cases may also be linked to an expanded geographic range for ticks.

With both the prevalence and geographic range of Lyme disease increasing, vaccination could help prevent the disease and ease its burden.

A vaccine candidate

In April of 2020, responding to this need, Pfizer Inc and Valneva SE announced a collaboration to develop VLA15 (6), an innovative vaccine candidate against Lyme disease. There are currently no approved human vaccines for Lyme disease. With two Phase 3 trials in progress, VLA15 is the most advanced Lyme disease vaccines candidate currently in clinical development.

VLA15 targets the outer surface protein A (OspA) of Borrelia burgdorferi, inhibiting its ability to infect humans. The vaccine has a unique mechanism whereby, once vaccinated, the recipient generates antibodies against the OspA protein and, after receiving a tick bite, the antibodies go into the feeding tick along with the blood meal and neutralize the Borrelia bacteria, preventing it from being transmitted to the host and causing Lyme disease. Phase 2 trials demonstrated VLA15's safety and ability to generate strong immune responses in both adults and children.

A single type of Borrelia causes almost all the Lyme disease in the U.S. However, in Europe, there is a broader range of variants, including the U.S. species (4). VLA15 has been designed to offer coverage for the most common circulating types of Borrelia bacteria that cause Lyme disease in both regions. This vaccine holds promise not only for preventing Lyme disease but also for addressing its increasing geographic spread and diagnosis rates. This alum-adjuvanted, intramuscular formulation covers the six most common OspA serotypes in North America and Europe.

Phase 3 clinical trials

Building on successful Phase 1 and 2 clinical trial results, Pfizer Inc. and Valneva SE announced that they have completed recruitment for Phase 3 trial Vaccine Against Lyme for Outdoor Recreationists (VALOR) (NCT05477524) for Lyme disease vaccine candidate VLA15 (7).

The Phase 3 VALOR trial, which initiated in August of 2022, aims to confirm the vaccine's efficacy, safety, and immunogenicity in 9,437 participants aged five and older across endemic regions in the U.S., Europe, and Canada. As part of the primary series, participants receive three doses of VLA15 or a saline placebo (1:1 ratio) within the first year, and one booster dose approximately one year after completion of the primary immunization (8).

The VLA15 candidate has demonstrated a strong immune response and had a favorable safety profile across all dose and age groups in pre-clinical and clinical trials so far. No vaccine-related serious adverse events (SAEs) and no safety concerns were observed by an independent Data Safety Monitoring Board (DSMB) (9). A second Phase 3 trial (C4601012), aiming to provide further evidence on the safety profile of VLA15 in the pediatric population, is also fully recruited.

The VALOR trial is expected to be concluded by the end of 2025. Subject to positive Phase 3 data, Pfizer and Valneva aim to submit a Biologic License Application to the Food and Drug Administration and Marketing Authorization Application to the European Medicines Agency in 2026.

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VACCINES BEAT

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At Vaccines Beat, we understand that vaccines and immunization have become a crucial topic of discussion at the center of any public health analysis. Therefore, timely, relevant, accessible, and well-curated information for all vaccine preventable diseases is key to advancing better health policies.

For this reason, a team of passionate vaccine professionals has created Vaccines Beat and each month diligently works to share with the healthcare ecosystem information, knowledge, and insights to improve global health.

Vision

Vaccines Beat aims to become the beacon of insight in the public health ecosystem through its distinctive monthly newsletter. With an in-depth 360 perspective, carefully curated information and expert analysis, this novel platform fosters collaboration among a diverse global network of stakeholders.

Mission

Vaccines Beat's main task is to inform through the review of the most recent developments in vaccines, immunization, and vaccine preventable diseases. Our mission extends to sharing best practices from successful initiatives worldwide while building bridges through editorial collaboration with regional and international stakeholders.

Vaccines Beat highlights the importance of information sharing & collaborative efforts within the public health community to boost vaccination campaigns, R&D, public policy, access, awareness, and equity.

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