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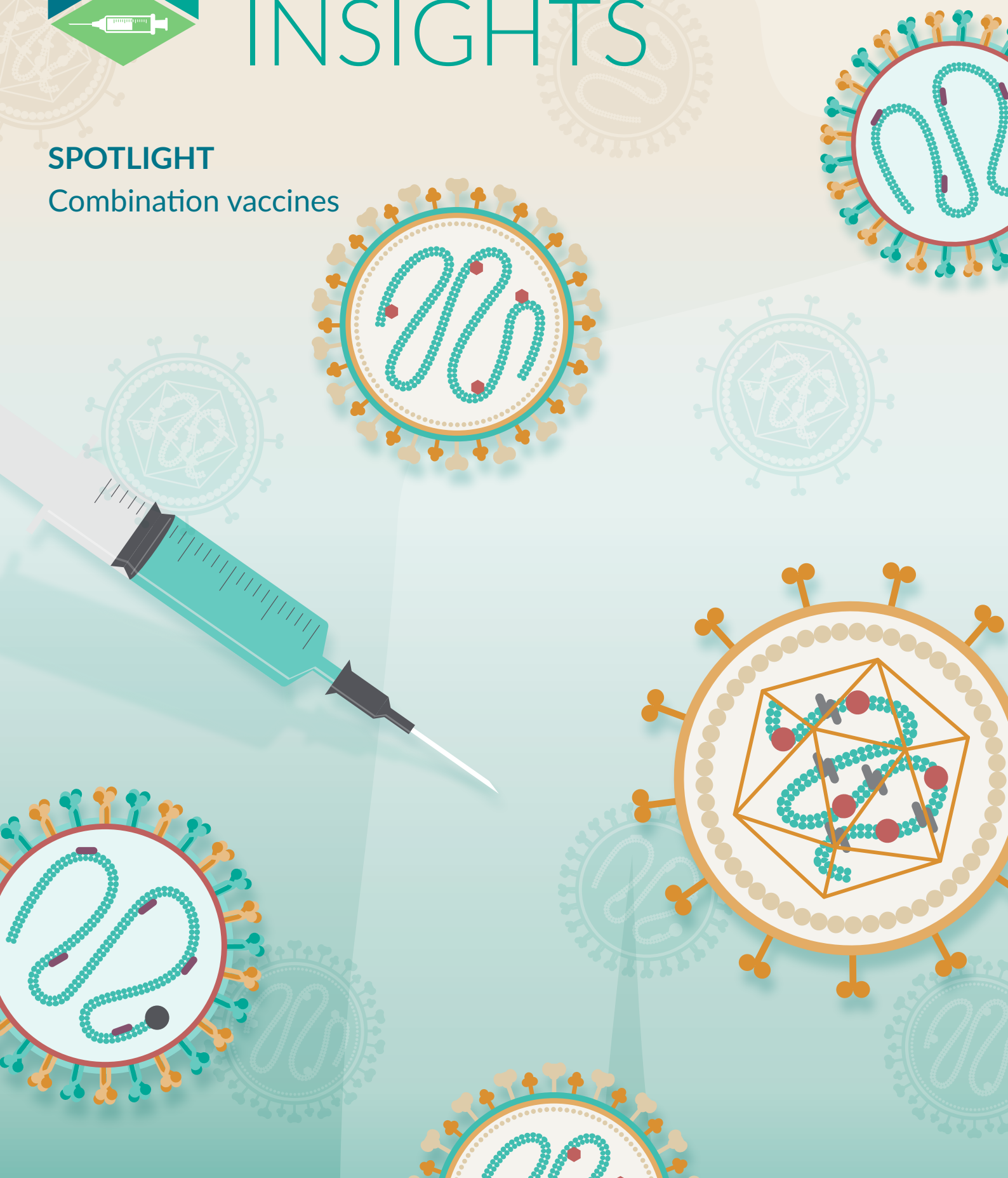
VACCINE INSIGHTS

SPOTLIGHT

Combination vaccines



VACCINE INSIGHTS

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Combination vaccines

The case for combination vaccines

INTERVIEW

"...combinations are likely to increase acceptance and lead to higher vaccination coverage."

As immunization schedules grow ever more crowded, combination vaccines could reduce costs and complexity, yet very few are being developed. **William Hausdorff**, Lead, Vaccines Public Health Value Proposition and Meningococcal Vaccine Development, PATH, has been at the center of efforts to kickstart development of new combination vaccines. **Charlotte Barker**, Commissioning Editor, *Vaccine Insights*, caught up with Hausdorff to discuss clarifying policy, incentivizing developers, and what makes a successful combination.

Vaccine Insights 2025; 4(1), 11–16 · DOI: 10.18609/vac.2025.002

Q What led you to your recent work on combination vaccine policy?

WHI am a biochemist by training with extensive experience in epidemiology. I've worked in vaccine development and evaluation for around 30 years for organizations including USAID, major pharmaceutical companies, and a nonprofit. I now work at PATH, an international health NGO, focused on vaccination policy and development of new vaccines.

Having approached vaccines from many different angles, it's always been clear to me that vaccines only have value if they are being widely used. Throughout all the threads of my career, I have asked 'what does it take to get vaccines to be adopted and used?' Part of it is having the right vaccines, the ones countries want, available at an affordable price, but it is also the way they are developed and put together.

"The concept of creating clinical syndromic combinations may have particular advantages."

That brings us to the issue of combination vaccines. On the one hand, we now have many safe and effective vaccines, which is tremendous. But it comes at a cost of an increasingly crowded childhood vaccination schedule, with many more in the pipeline. Only a few vaccines are currently available in combinations, and it is not at all clear how and whether the large number of single-pathogen, standalone vaccines currently in development could be adopted and be introduced into immunization programs. It's not a sustainable situation.

Q What are some of the advantages of combination formulations?

WH Along with crowded vaccine schedules, large number of injections may dissuade patients or their caregivers from getting all their shots, so combinations are likely to increase acceptance and lead to higher vaccination coverage. Combination vaccines could also alleviate the storage and administration costs of multiple separate injections (or multiple oral doses).

Not so commonly understood are the risks to healthcare workers preparing multiple different vaccines. Each new vaccine increases the risk of human error, such as incorrect preparation or administration, wasted doses, and needle-stick injuries.

Notably, there are certain important vaccine candidates that will likely never be used unless they are part of a combination. Good examples include those targeting various antibiotic-resistant bacteria. These are dangerous pathogens, but the morbidity and mortality attributable to any single pathogen, such as *Shigella* or *Salmonella enterica* (specifically the paratyphoid serovar), which cause enteric disease, or others like *Klebsiella* and *Acinetobacter* that cause neonatal sepsis, is likely not enough to justify a spot in already-crowded vaccination schedules. However, in combination, they could be more attractive and make an important difference to a growing problem.

The concept of creating clinical syndromic combinations may have particular advantages. For example, acute otitis media (middle ear infections), can be bacterial or viral, and it is virtually impossible to differentiate between the two without tympanocenteis. Hence, in many locales, when a doctor sees a child with an ear infection, they tend to prescribe antibiotics 'just in case' since the child (and parent!) is suffering. However, if the child was known to have been vaccinated against all of the major bacterial causes of otitis media (with a hypothetical combination 'otitis media vaccine'), the doctor and parents could feel more confident that the infection is viral and take a 'wait and see' approach, reducing the risk of antimicrobial resistance and avoiding side effects.

There are multiple pathogens that lead to malnutrition and growth stunting in resource-constrained settings, such as *Shigella*, *Escherichia coli*, and *Campylobacter*. A combination vaccine against those three pathogens could make a much more significant dent in growth faltering and stunting than any of the individual vaccines, especially if the organisms are synergistic in their effects.

Syndromic combinations also have the advantage of easier communication. Telling a patient or caregiver you want to vaccinate against *Hemophilus influenzae* type b may not mean much to them, but a vaccine against the major causes of pneumonia is more easily understood.

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Q There is broad agreement that we need new combination vaccines, but few are in development. What hurdles do developers face?

WH Existing combination vaccines such as DTaP (diphtheria, tetanus, and acellular pertussis) and MMR (measles, mumps, and rubella) have been tremendously successful in improving public health. So why aren't there more?

The very few combination vaccines in advanced clinical development are mainly focused on respiratory diseases in adult populations, such as flu, RSV, COVID, and metapneumovirus. But the few others in development are still at an early stage and suffer from a dearth of significant investment from vaccine developers. The answer can only be that developers don't see other combinations as a great market opportunity—the risk–benefit ratio is not favorable. Several factors contribute to the issue, both on the risk and the benefit sides.

Firstly, the risks are greater. Put simply, it is harder to make combinations than single-pathogen vaccines. Developers have to deal with ensuring physicochemical compatibility and other formulation challenges due to differences in adjuvants, excipients, not to mention the vaccine antigens themselves. Developing analytical assays to ensure consistency and quality is also harder with a complex mixture.

Having produced a combination vaccine, the next hurdle is demonstrating efficacy, which for many vaccines is often assessed by measuring the immune response elicited. Yet regulatory pathways have been designed with mono-pathogen vaccines in mind, with the emphasis on proving efficacy (and of course, safety) of each and every component with a high degree of certainty. But clinical studies for combination products are more complex by definition. With immune responses to multiple components to measure simultaneously, it is harder to demonstrate immunological non-inferiority with statistical significance, crucial because immune interference—sometimes with unknown, if any, clinical implications—has doomed a number of vaccine candidates in the past.

On the benefit (demand) side, there is a lack of clarity about whether combination vaccines, even if successfully developed, will be recommended, and purchased. Vaccine adoption and use by immunization programs is highly dependent on recommendations from national, regional, and global immunization advisory committees, such as ACIP in the USA, JCVI in the UK, or SAGE for the WHO. Currently, these bodies generally do not express preferences for combinations over their respective mono-pathogen standalone vaccines, or issue recommendations as to which vaccines should be combined in the future. This means there is limited incentive for a vaccine developer to take the greater risk of producing a new combination.

Q Why has there been a seeming reluctance from public health bodies to express a clear preference for combination over single-pathogen formulations?

WH One issue is that governments and funders want to encourage competition in the vaccine market and are therefore reluctant to favor one product over another, provided the efficacy and safety are the same. While this is clearly an important concern, the lack of any preference implies that the combination

"The challenges are complex and daunting but there is a will among regulators and policy agencies to address this."

vaccine is simply not valued by the advisory committees, despite the multiple benefits to the immunization program and public health.

The sheer complexity of assessing combination vaccines may also be a factor. The value of individual vaccines can be measured by reductions in morbidity and mortality, whereas there are additional factors to consider for combination vaccines. For example, what is the value of combining a vaccine with low uptake, such as the typhoid conjugate vaccine, with a vaccine that has high uptake, such as measles? What is the value of combining two currently administered vaccines, thus creating space in the vaccination schedule for an additional vaccine to be given at the same time, such as malaria? What is the value of a vaccine that has synergistic effects, such as the syndromic combinations I mentioned earlier?

The calculations are complex and will require some creative thinking to decide how combinations should be prioritized and their value measured.

Q Are we starting to see action to address some of these issues? How is PATH involved?

WH Combinations are increasingly talked about in immunization and global policy circles. The challenges are complex and daunting but there is a will among regulators and policy agencies to address this.

PATH is working with the WHO to take on the policy aspect and clarify what combinations are most needed in the public health space so that developers can have more confidence on the demand side. We are working with regional immunization advisory groups to put together a policy decision-making framework for combinations that make sense in terms of existing immunization programs (e.g., similar number of doses and given at similar ages) and technical limitations (e.g., identical route of administration and physico-chemical compatibility). We are also working to develop a set of metrics to evaluate the value of combinations more accurately.

Over the next 2 years, we plan to present our proposals to various advisory and policy committees, including Regional Immunization Technical Advisory Groups (RITAGs) and WHO advisory committees including SAGE, to get feedback and (hopefully) buy-in.

We are also trying to start the regulatory debate. We believe lessons can be learned by the regulatory approach for pneumococcal conjugate vaccines, which are mono-pathogen combinations made up of 10, 13, 20, or more individual conjugates against different strains. Regulators accepted that it would not be feasible to prove the individual efficacy of every component (particularly minor strains) in clinical trials, but instead recognized the overall value of the vaccine. They therefore accepted other, more indirect, and frankly less precise indications of efficacy for each serotype. More detailed effectiveness information on individual subtypes is being collected and analyzed post-licensure, so that future versions of the vaccine can be optimized. Crucially, there was of course absolutely no compromise on the safety profile of the combination vaccine vs individual

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components. We hope the same mentality can be applied to multi-pathogen combination vaccines.

As a first step, we will be hosting a meeting on the outskirts of the Global Vaccine and Immunization Research Forum in Rio this March, bringing together regulators and developers to discuss regulatory issues for combination vaccines.

Q What emerging or developing technologies could help advance combination vaccines in the future and improve uptake?

WH mRNA vaccines are promising in this regard since the platform allows combination of different antigen sequences on a single mRNA, or several mRNAs, within the same formulation.

Microarray patches are another way to deliver multiple antigens with or without physical mixing. There is some promising work on MR vaccination using microarray patches.

While these and other technologies should help in the formulation aspect of simultaneously administering vaccines targeted at multiple pathogens, it's important to note that the regulatory and policy challenges of such combinations remain similar to those developed with other technologies.

On the immunology side, researchers are working to gain a better understanding of the immune correlates of protection. That would be of great value for combination vaccines, as it could allow assessments of vaccine efficacy without the need for prohibitively large clinical efficacy studies.

Q Do you foresee challenges to caregiver/patient acceptance of novel combination vaccines?

WH Potentially, yes. On the one hand, you would expect fewer injections to increase acceptance, and we believe it will. However, certain combination vaccines (notably MMR) have sometimes been singled out by those spreading vaccine disinformation and spuriously linked to serious side effects despite lack of credible scientific evidence. So, it's not a given that acceptance will be higher for combination vaccines, and it will be important to ensure that the public understands the case for combinations.

BIOGRAPHY

William Hausdorff is Lead, Meningococcal Vaccine Development and Vaccine Value Propositions at PATH's Center for Vaccine Innovation and Access, Washington, DC, USA. Originally trained as a biochemist at the Johns Hopkins University, the US National Institutes of Health, and Duke University, Bill has worked on the development, clinical evaluation, registration, implementation, and post-marketing assessment of a wide range of vaccines to prevent major public health problems for 30 years. His vaccine career started with the US Agency for International Development and the Centers of Disease Control and Prevention in Washington, DC, USA and Cairo, Egypt, where he worked to expedite

introduction of new vaccines into developing country immunization programs. This was followed by two decades at Wyeth Vaccines and GlaxoSmithKline Vaccines where Bill held a variety of roles in the Scientific Affairs & Research Strategy and Epidemiology Groups, and as a Vaccine Development Leader. For the past 6 years he has been based at the international health NGO PATH and also serves as Professor within the Faculty of Medicine, Université Libre de Bruxelles, Belgium. Bill is recognized for his significant contributions to the development of highly effective pneumococcal conjugate vaccines at each of the companies, and as the author of over 100 scientific articles and book chapters, including a recent commentary review in *Lancet Global Health* on the need for and challenges to combination vaccine development and use. He currently serves on WHO's Product Development Vaccine Advisory Committee (PDVAC) as well as the WHO Technical Advisory Group on Vaccines and Antimicrobial Resistance.

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COMBINATION VACCINES

SPOTLIGHT

The promise and predicament of combining adjuvants in vaccines

Ari Joffe

VIEWPOINT

"At this time, the only way to gain confidence in a novel combination adjuvant is through direct testing of the combination during preclinical vaccine development..."

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Combination vaccines—that is, vaccines targeting two or more pathogens within one vaccine formulation—have the potential to improve human health by reducing the number of required shots and, thus, improving vaccine uptake. This outcome is certainly worthy of pursuit, but formulating combination vaccines is much more complicated than simply mixing two or more existing vaccines together. An ideal combination vaccine should contain an optimized mixture of antigens and adjuvants in a well-characterized formulation that provides safe and efficacious protection from disease. While many vaccines are composed of either live-attenuated or killed whole pathogens, vaccine developers have recently moved toward vaccine formulations with subunit or genetically encoded antigens [1] because their simple nature offers benefits that address safety and regulatory concerns. Such vaccines typically require the addition of exogenous adjuvants to elicit an immune response and subsequent protection. For a novel subunit combination vaccine, it is likely

that optimized protection will require antigens from multiple pathogens and multiple adjuvants in a final formulation. While the combination of vaccine antigens presents many opportunities and challenges, the remainder of this article will focus on considerations around combinations of vaccine adjuvants (combination adjuvants) within novel vaccine formulations.

Individual vaccine adjuvants can skew an immune response toward a particular immune phenotype. For example, vaccines adjuvanted solely with aluminum salts ('alum') are known to induce characteristics of a Th2 response, while toll like receptor (TLR) agonists such as CpG or MPL tend to skew toward a Th1 response. Still other adjuvants may trigger immune responses with different immune profiles. Examples of immune profiles induced by various adjuvants can be viewed at the US National Institute of Allergy and Infectious Diseases' (NIAID) Vaccine Adjuvant Compendium [2].

One method to fine-tune the immune profile of a vaccine is to combine vaccine adjuvants with complementary profiles (akin to seasoning a cooked dish with salt, pepper, and spices). However, the immunogenic result of combining adjuvants has proven to be unpredictable. Observations from both in vivo and in vitro model systems have demonstrated that the adjuvant effect of combination adjuvants can be classified as one of three possibilities: synergistic, antagonistic, or additive. The synergistic—and often most desirable—case describes situations where a combined adjuvant effect is enhanced beyond simple addition of the individual adjuvant effects. For example, the combination of a TLR4 agonist and QS-21 adjuvant has been shown to elicit a synergistic immune profile with greater complexity than one would expect by combining the individual profiles of each component [3,4]. Instances of adjuvant antagonism encompass situations where the strength of an immune response induced by combination adjuvants is diminished when compared to the strengths of the individual components. As an example, a combination of TLR4 and Dectin-1 has been shown to diminish IL-1β, TNF-α, and IL-6 cytokine production below the levels induced by each adjuvant alone [5]. Finally, the additive case describes situations where the immunogenic effects of the individual adjuvant components are preserved in a combination adjuvant formulation and the resulting immune profile represents what would be predicted by adding the individual profiles together. When the combination of two or more adjuvants is known to be additive, the immune profile of a novel vaccine using this combination is more straightforward to predict. An encouraging finding from Pandey et al., indicates that for combinations of three or more adjuvants, immune responses become additive of the responses conferred by the single adjuvants and their pairs—meaning that a thorough characterization of single adjuvants and pairs of adjuvants may be sufficient for predicting outcomes of higher-order combinations [6].

The unpredictability of how adjuvants will work in concert represents an obstacle for the rational design of vaccines. At this time, the only way to gain confidence in a novel combination adjuvant is through direct testing of the combination during preclinical vaccine development, which can be costly and time consuming. Improved understanding of the molecular and cellular pathways being induced by adjuvants (both individually and in combination) is needed to overcome this bottleneck. Adjuvant researchers can approach this problem from several different angles: directly study and profile the mechanisms of action for adjuvant combinations both in vitro and in vivo; and develop and apply new computational models that predict immune outcomes based on new and/or existing data from studies using combination adjuvants. The first approach is the inspiration for the NIAID Molecular Mechanisms of

Combination Adjuvants (MMCA) Program [7], while the second approach has been described in a few recent publications [8,9]. Regardless of the approach taken, scientific advances in this arena are needed to accelerate the rational design of optimized, effective, and safe vaccines.

It is important to note that researchers interested in studying the complex topic of combination adjuvants will need to closely consider the entire vaccine formulation and not just the adjuvant components. Correct interpretation of results critically hinges on a thorough characterization of the vaccine formulation being studied. At a minimum, a vaccine formulation consists of antigen(s), adjuvant(s), and various excipients (e.g., carriers, stabilizers, and buffers). Each of these components can have varied interactions with one another depending on the vaccine formulation. Researchers will not be able to understand and predict how combination adjuvants work without a comprehensive physiochemical characterization of the formulation (e.g., encapsulation of adjuvant/antigen in a carrier, electrostatic interactions between vaccine components, stability over time and in relevant environments). Furthermore, vaccine regulators, such as the US FDA, consider a vaccine product to be the entire formulation, and do not focus on just one component. Because of this, vaccines containing a novel combination of adjuvants should not be considered as de-risked because one or both adjuvants have been approved in other licensed vaccine formulations.

While many gaps remain in our current ability to predict how novel combination adjuvants may affect vaccine responses, the reward for solving this problem could be immense. Accurate models predicting adjuvanticity of multiple adjuvants will enable rapid rational design and fine-tuning of an immune response for a specific indication—ultimately supporting the development of a new class of safe and protective vaccines to improve human health.

REFERENCES

1. Plotkin S. History of vaccination. *Proc. Natl Acad. Sci. USA* 2014; 111, 12283–12287.
2. NIAID Vaccine Adjuvant Compendium. https://vac.niaid.nih.gov (accessed Feb 2025).
3. Coccia M, Collignon C, Hervé C, *et al.* Cellular and molecular synergy in AS01-adjuvanted vaccines results in an early IFNgamma response promoting vaccine immunogenicity. *NPJ Vaccines* 2017; 2, 25.
4. Dendouga N, Fochesato M, Lockman L, Mossman S, Giannini SL. Cell-mediated immune responses to a varicella-zoster virus glycoprotein E vaccine using both a TLR agonist and QS21 in mice. *Vaccine* 2012; 30, 3126–3135.
5. Timmermans K, Plantinga TS, Kox M, *et al.* Blueprints of signaling interactions between pattern recognition receptors: implications for the design of vaccine adjuvants. *Clin. Vaccine Immunol.* 2013; 20, 427–432.
6. Pandey S, Gruenbaum A, Kanashova T, *et al.* Pairwise stimulations of pathogen-sensing pathways predict immune responses to multi-adjuvant combinations. *Cell Syst*. 2020; 11, 495–508.
7. NIAID Molecular Mechanism of Combination Adjuvants (MMCA). https://www.niaid.nih.gov/research/molecular-mechanism-combination-adjuvants (accessed Feb 2025).
8. Chaudhury S, Duncan EH, Atre T, *et al.* Identification of immune signatures of novel adjuvant formulations using machine learning. *Sci. Rep.* 2018; 8, 17508.
9. Tang Y, Kim JY, Ip CKM, *et al.* Data-driven discovery of innate immunomodulators via machine learning-guided high throughput screening. *Chem. Sci.* 2023; 14, 12747–12766.

BIOGRAPHY

Ari Joffe is a Program Officer at the US National Institute of Allergy and Infectious Diseases (NIAID). He manages a portfolio of research programs, grants, and contracts on various topics relating to fundamental immunology. This includes research projects investigating the discovery, development, and mechanisms of action of vaccine adjuvants.

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COMBINATION VACCINES

SPOTLIGHT

mRNA combination vaccines for respiratory infections: the developer's view

INTERVIEW

"...combining targets by symptoms allows for a more integrated approach to seasonal vaccination campaigns..."

Charlotte Barker, Commissioning Editor, *Vaccine Insights*, catches up with **Francesca Ceddia**, Chief Medical Affairs Officer, Moderna, to learn more about the company's efforts to develop mRNA-based combination vaccines against COVID-19, RSV, and influenza.

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Q What is your background in the vaccines space?

FC I have been working in the vaccine space for more than 20 years and have contributed to the development and introduction of a number of vaccines, including combination vaccines, particularly in the pediatric space. I joined Moderna during the pandemic, where I could experience firsthand the advantages of the mRNA technology platform in vaccine development, including its remarkable flexibility and the possibility to combine different antigens in a single vaccine. Over these past 3 years, I've been deeply involved in Moderna's journey to develop and deploy mRNA vaccines, including our COVID-19 vaccine, which demonstrated the platform's scalability and impact.

"...we are leveraging the mRNA platform to explore new frontiers, including oncology and rare diseases."

Beyond COVID-19, during this period, we have licensed an mRNA-based RSV vaccine, and progressed a number of vaccines in development, both in the respiratory space—such as combination vaccines for COVID-19, RSV, and influenza—and in other infectious disease fields.

Q What are you working on right now?

FC Our focus is to highlight the broad versatility of the mRNA platform. While we continue to prioritize our respiratory portfolio, we currently have two significant Phase 3 programs underway. One addresses CMV (cytomegalovirus) disease, a leading cause of birth defects globally, and the other targets norovirus, a critical public health concern. The norovirus program is particularly timely, as many countries are experiencing a peak in cases this season. In parallel, we are advancing Moderna's next-generation vaccine programs, particularly in developing combination vaccines for respiratory viruses like COVID-19, influenza, and RSV. These combination vaccines aim to provide broader protection in a single shot, enhancing convenience and improving patient adherence to vaccination. Beyond infectious diseases, we are leveraging the mRNA platform to explore new frontiers, including oncology and rare diseases. At the same time, we are optimizing formulations (e.g., to improve storage conditions), addressing pressing global health challenges and expanding access to RNA vaccines worldwide.

Q What is Moderna's approach to combination vaccines?

FC Moderna's approach to combination vaccines is rooted in the flexibility of mRNA technology, which allows us to encode multiple antigens in a single vaccine. This capability enables us to target multiple pathogens or strains with a single product. Currently, our pipeline includes combination vaccines like our investigational flu–COVID-19, flu–RSV, and flu–COVID-19–RSV combination candidates. These aim to provide comprehensive respiratory virus protection. We are also exploring incorporating additional respiratory pathogens, such as human metapneumovirus (hMPV), to offer even broader protection.

Q Can you outline the hurdles facing developers in getting combination vaccines to market?

FC Combination vaccines pose unique scientific challenges, particularly in formulation. Each antigen in the vaccine must remain stable and immunogenically effective without interfering with the others. For mRNA vaccines, this means ensuring that the lipid nanoparticles deliver all encoded antigens effectively and that the immune

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response is balanced across multiple targets so that no single antigen's immunogenicity overshadows another's. Historically, there have been numerous attempts to develop combination vaccines or add additional antigens to existing vaccines, but many of these efforts have faced significant challenges, including formulation instability, manufacturing complexity, and reduced efficacy of certain antigens.

With mRNA technology, many of these challenges are reduced because the platform offers great flexibility in design and production. Each antigen is encoded by a separate mRNA sequence, allowing precise control over the expression levels of each target protein. This modularity ensures that all encoded antigens are produced reliably in the body, minimizing interference between antigens. Additionally, mRNA vaccines utilize a single, consistent manufacturing process regardless of the number of antigens included, simplifying production and reducing the risk of formulation instability. Furthermore, the ability to rapidly iterate and optimize mRNA sequences allows developers to fine-tune combinations more efficiently than with traditional vaccine platforms, significantly accelerating development timelines. By addressing these historical barriers, mRNA technology opens new possibilities for effective and scalable combination vaccines.

From a regulatory standpoint, combination vaccines require comprehensive data to demonstrate safety, immunogenicity, and efficacy for each antigen. This often involves larger, more complex clinical trials than single-pathogen vaccines. Additionally, harmonizing regulatory requirements across countries can delay development, as policies on combination vaccines vary globally.

Particularly where the standalone vaccines are currently produced by different companies, healthcare providers and patients may be skeptical of new combination vaccines if they are already comfortable with existing standalone vaccines. Therefore, if the market is dominated by established standalone vaccines, switching to a combination product may require extensive education and marketing efforts. Additionally, some public health organizations prefer single-antigen vaccines because they allow more flexibility in immunization schedules.

Q What would make it easier for companies to develop and commercialize combination vaccines?

FC There are several enablers:

1. **Collaborative frameworks:** partnerships between companies could help streamline development when different organizations own the individual vaccine components.
2. **Regulatory harmonization:** clear and consistent global guidelines specific to combination vaccines would reduce complexity.
3. **Technological advances:** platforms like mRNA, which allow for modular and scalable development, could simplify the process of designing combination vaccines.
4. **Incentives for innovation:** governments and global health organizations could play a role by offering funding or fast-track pathways for high-priority combination vaccines.

"...mRNA vaccines can quickly respond to emerging threats, allowing faster iterations of combination products."

Q What are the specific benefits and challenges of combining mRNA vaccines?

FC There are several key benefits in utilizing the mRNA technology platform. Starting with flexibility, mRNA allows for encoding multiple antigens in a single lipid nanoparticle, enabling rapid design of combination vaccines. Another advantage is in terms of scalability: manufacturing processes are largely the same, regardless of the antigen combinations. Finally, speed: mRNA vaccines can quickly respond to emerging threats, allowing faster iterations of combination products.

The challenges are not specific to mRNA, but largely apply to traditional technologies too, for example:

- Formulation: ensuring that each antigen maintains its stability and desired immunogenicity.
- Dosing: determining the optimal dose for each antigen in a combination product without compromising efficacy or safety.
- Immunological interference: balancing immune responses to prevent one antigen from eliciting a disproportionately strong or weak response.
- Potential for increased reactogenicity.

Q What are the advantages of combining vaccine targets by symptoms, as Moderna is doing for respiratory viruses?

FC Combining vaccines by symptoms—such as targeting respiratory viruses—has significant public health and patient-centric benefits. From a public health perspective, a single vaccine protecting against multiple respiratory pathogens simplifies immunization schedules, improves coverage rates, and reduces the logistical burden on healthcare systems. For patients, it reduces the number of injections, enhancing convenience and compliance. Additionally, combining targets by symptoms allows for a more integrated approach to seasonal vaccination campaigns, aligning protection strategies for viruses that often co-circulate.

Q What's next for combination vaccines?

FC For Moderna, the immediate focus is advancing our respiratory combination vaccine programs and exploring next-generation combinations that include pathogens like hMPV. Beyond respiratory viruses, there is potential to create combination vaccines for broader indications, such as endemic diseases or pediatric immunizations.

In the broader field, I anticipate a growing emphasis on personalized combination vaccines tailored to individual or regional needs. Advances in AI and genomic tools will likely

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accelerate vaccine design and allow for more precise antigen selection. Overcoming regulatory and commercialization barriers will also enable wider adoption, paving the way for a future where combination vaccines are the standard rather than the exception for adults, as is already the case in the pediatric space.

BIOGRAPHY

Francesca Ceddia is a distinguished medical professional and the current Chief Medical Affairs Officer at Moderna, Cambridge, MA, USA. In her role, she is responsible for leading, developing, and executing the company's global medical and evidence generation strategy, shaping the future of Moderna's mRNA technology pipeline across infectious diseases, oncology, and rare diseases. A medical doctor by training, Francesca specialized in respiratory diseases at the University of Siena, Italy. After a period of practicing pulmonology, she transitioned into the pharmaceutical sector, where she has since held a range of roles of increasing responsibility across clinical, vaccine development, access, and medical affairs. Throughout her career, Francesca has worked in several therapeutic areas, and her work has been instrumental in leading the development of various vaccine candidates. She has been deeply involved in the medical strategy across numerous infectious disease areas, with a particular emphasis on combination/multicomponent vaccines. Her contributions to the field are well-documented in peer-reviewed publications. More recently, Francesca has been dedicated to addressing vaccination gaps across all age groups. Her work has been pivotal in responding to the vaccination needs of older adults, further solidifying her commitment to global health and patient care.

Francesca Ceddia, Chief Medical Affairs Officer, Moderna, Cambridge, MA, USA

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COMBINATION VACCINES

SPOTLIGHT

Prospects for an adult combination respiratory vaccine: the clinician's view

Angela Branche

VIEWPOINT

"...it seems very likely that mRNA will be one of the tools that helps us to develop new combination vaccines, especially against respiratory viruses."

With vaccination against influenza, SARS-CoV-2, and RSV now recommended for at-risk adults, momentum is building for new combination respiratory vaccines. However, the path to the clinic remains challenging. Here, I outline some of the key benefits and complexities of bringing combination vaccines to market—from the perspective of a respiratory medicine clinician and researcher.

On January 28, 2025, Charlotte Barker, Commissioning Editor, *Vaccine Insights*, spoke to Angela Branche, Associate Professor of Medicine, University of Rochester, about the concept of an adult respiratory virus combination vaccine and the difficulties of taking combination vaccines into clinical trials. This article has been written based on the interview.

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Until recently, combination vaccines have not typically been needed for adults. Unlike children, who are immune-naïve and need to be protected against multiple serious pathogens early in life, adult vaccinations have typically been fewer in number and on a less rigid schedule. Consequently, combination vaccine development has not been a major priority.

However, in the past 20 years, the vaccine field for adults has become more crowded. We are now entering a new phase of disease prevention, aiming to protect people against multiple different respiratory viral and bacterial pathogens each winter. Specifically, we are now trying to protect at-risk adults against contracting and becoming seriously ill with influenza, respiratory syncytial virus (RSV), and SARS-CoV-2 while still maintaining high uptake of scheduled vaccines against non-seasonal pathogens like *Streptococcus pneumoniae*.

Administering three seasonal vaccines in a single sitting is unlikely to be well accepted by patients or clinicians, so combination respiratory virus vaccines are increasingly desirable, for adults as well as children.

THE POWER OF COMBINATIONS

Combinations have a number of important advantages over separate vaccines. For adult respiratory vaccines, the key is vaccine acceptance. Numerous studies in children have shown that when you vaccinate against multiple different pathogens with one shot, your ability to protect and prevent disease from those pathogens increases quite dramatically. If we want to have the best preventative strategies going forward, combination vaccines offer us that possibility.

Without combination vaccines, clinicians have to choose which vaccines to recommend or strongly recommend, recognizing that for some patients all of those vaccines are potentially equally important. If September is the only time you see your patient for the year and they need routine herpes zoster and pneumococcal vaccines, plus seasonal flu, COVID-19 and, RSV, you are looking at giving 3–5 vaccines in one appointment.

Reactogenicity is a big driver of both vaccine acceptance and administration. Clinicians prefer not to co-administer several of the more reactogenic vaccines to their patients because they know that if the patient becomes unwell, it could lead to vaccine hesitancy in the future. Therefore, there is a lot of interest in combinations that could streamline the vaccination schedule.

CLINICAL DEVELOPMENT COMPLEXITY

For all combination vaccines, you first have to identify the right antigen to protect against a single pathogen, before combining the antigens and finding a stable formulation. Then you have to test the immunogenicity of that combination vaccine relative to the immune response to a single-antigen vaccine.

This process is more rigorous and more staged now than when the first combination vaccines were developed, incorporating reactogenicity, rare side effects, and immune interference. Essentially, the goal is to find the right doses of the individual components to achieve good immune responses without any safety issues. It's a balancing act and requires a complex process of dose finding and escalation.

Accordingly, researchers have to simultaneously answer several questions. Does combining antigens change the reactogenicity profile, safety, immune response, or efficacy in any way? If you see a safety signal from a combination vaccine, is that unique to the combination or true for one of the individual antigen components?

Secondly, to what are you comparing the immunogenicity or efficacy of

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the combination vaccine? There is a lot of complexity. Some recent studies have demonstrated there is a small impact on immune responses against influenza when flu and COVID vaccines are given in combination or sequentially on the same day. Is that clinically meaningful? It's hard to know.

Right now, developers must prove non-inferiority of combination vaccines in comparison to the standalone vaccines, often based on statistical considerations around the immune response. It is an appropriate methodology, but leaves a lot of unknowns in terms of clinical relevance and does not factor in the additional benefits of combinations in terms of acceptance, logistics, etc.

The only way to show clinical relevance is with efficacy trials, which poses ethical challenges. Can you justify not giving patients either a flu or COVID-19 shot in order to carry out an efficacy trial of a COVID-19–flu combination vaccine?

A combination vaccine gives us the best chance of getting the most people protected against multiple different diseases. If a statistically inferior immunogenicity result (which may or may not be clinically relevant) halts development of a combination vaccine, we lose the ability to provide the optimal vaccine strategy.

Often, multi-valent vaccines for single pathogens (e.g., influenza, pneumococcal disease) protect better against some strains of the disease than others. I think we can take a lesson from that for multi-pathogen combination vaccines—you might lose some immunogenicity compared with standalone vaccines, but you gain an overall product that optimizes prevention of disease, which is the ultimate goal of all vaccine programs. In other words, we may need to accept a degree of imperfection, in order to get the best possible clinical outcome.

LOOKING AHEAD

Looking at current development pipelines, it seems very likely that mRNA will be one of the tools that helps us to develop new combination vaccines, especially against respiratory viruses. The robust serological immune response achieved with a small amount of mRNA makes the modality well suited to multiple antigens. There is a risk of high reactogenicity, but developers are now working on adapting their formulation to offset that. Several companies are exploring influenza and SARS-CoV-2 combination vaccines, and potentially even incorporating RSV and/or human metapneumovirus.

BIOGRAPHY

Angela Branche is an Associate Professor of Medicine at the University of Rochester, Rochester, NY, USA. Dr Branche received her Bachelor of Arts degree in Biology at the University of Pennsylvania, Philadelphia, PA, USA and Doctorate in Medicine at American University of the Caribbean, Cupecoy, Sint Maarten. She completed residency in Internal Medicine at NYU Langone Hospital-Brooklyn, Brooklyn, NY, USA and infectious disease fellowship at the University of Rochester. She currently has a clinical inpatient practice comprised of both general infectious diseases and HIV medicine patients. During her years at the University of Rochester her focus in research involved the use of viral molecular and immunological diagnostic assays to explore the pathogenesis and host response to acute viral respiratory illnesses in adults. She is currently Co-Principle Investigator for the UR Vaccine Treatment and Evaluation Unit (UR VTEU) one of ten NIH funded network sites in the USA. Her current research activities explore clinical disease, pathogenesis, development of therapeutics and

vaccine biology related to infection with viral and bacterial respiratory pathogens. Studies include assessment of asymptomatic carriage of *Streptococcus pneumoniae* and the impact of pneumococcal vaccination, surveillance of epidemic influenza infections and immunologic mechanisms of protection following natural infection versus vaccination, the development of pandemic influenza vaccines, population-based studies of RSV infection, and the development of vaccine and anti-viral agents for RSV. She remains involved in the NIH and the University of Rochester research response to the recent COVID19 pandemic conducting natural history, therapeutic, and vaccine studies. She is a member of the Infectious Disease Society of America Public Health Committee and the NIH IDCRC Emerging Infections Expert Working Group. Dr Branche has published several peer-reviewed articles, reviews, and book chapters related to respiratory viral pathogens in adults.

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VACCINE INSIGHTS

IMMUNE RESPONSE UPDATE

Harnessing high-throughput approaches for bacterial vaccine development

INTERVIEW

"I don't see us becoming completely dependent on AI tools, but they can and will be a fantastic partner in vaccine discovery."

Charlotte Barker, Commissioning Editor, *Vaccine Insights*, talks to **Fadil Bidmos**, UK MRC Senior (Non-Clinical) Fellow and Proleptic Senior Lecturer in Bacterial Vaccinology in the Department of Infectious Disease at Imperial College London, about his lab's groundbreaking application of Reverse Vaccinology 2.0 in the meningococcal, pneumococcal, and gonococcal disease areas.

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Q How did you become interested in immunology and infectious disease?

FB I must admit, during my undergraduate days, I didn't plan to go into immunology or infectious diseases. My goal was autism research—to unlock, if they existed, the genetic cause(s) of autism spectrum disorder. But coming

from a research-driven household, with both my parents immersed in it professionally and personally, curiosity and scientific inquiry were second nature. That foundation made it easy to pivot when the time came. So, when I undertook an MSc in Molecular Genetics, and was assigned to a research project on the phenomenon of phase variation in *Campylobacter jejuni*—the most common cause of gastroenteritis in humans in the developed world—I embraced the challenge of a new field. Phase variation refers to the reversible switching of gene expression between states that are associated with high or low levels of the gene product (ON/OFF or high/medium/low)—this reversible switching can be controlled by the extension or shortening of the lengths of simple sequence repeat tracts, which occurs when errors made during DNA replication are not rectified. This research area of bacterial genetics was fascinating to me and resulted in some really nice data, which served to cement my interest in the field of infectious diseases—seeing the results of that project and working under the tutelage of an exceptional scientist, Professor Chris Bayliss, undoubtedly solidified my interest in bacterial genetics and infectious disease research.

Following my MSc, an opportunity arose in Chris's lab, to work on a study that explored the asymptomatic carriage of *Neisseria meningitidis*—a chief cause of bacterial meningitis, particularly affecting children aged between 6–24 months. The study aimed to elucidate the bacterium's evolution and ability to persist in the human host during carriage, and especially the contribution of genes whose expression was subject to phase variation. The project also encompassed adaptive immunity and antibody induction to the carried bacterial strain. This project focused my interest on meningococcal disease research, which became the subject of my PhD. 17 years later, I'm still in the field! I must add that it also helped that the meningococcal disease research community in the UK is one of the strongest in the world—unsurprisingly, we led the way globally in the introduction of the first protein-based meningococcal serogroup B (MenB) vaccine into the childhood immunizations schedule in 2015 [1].

Q How have your research interests evolved over the course of your career?

FB My research started in genetic epidemiology (the aforementioned carriage study) before transitioning to vaccine antigen discovery using a hypothesis-based approach for my PhD (iron acquisition proteins HpuAB ad HmbR) and higher-throughput approaches for the postdoctoral phase of my career. That general focus has remained consistent but the range of pathogens I am exploring has grown over the years to include *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*—a development enabled by the broad applicability of the evolving immunology research toolkit. My interests also extend to neighboring fields, such as antimicrobial resistance, vaccine immunology, and the application of synthetic biology approaches to enhanced vaccine precision and effectiveness.

"A lack of understanding of what constitutes the system of protection against certain pathogens…contributes to the inability to develop relevant *in vitro* surrogates of protection."

Q What are the most important immunological challenges standing in the way of novel and improved bacterial vaccines?

FB The fundamental challenge is the limitation of our knowledge. As humans, our intellect has its boundaries, meaning we will likely never fully resolve the complex immunological questions that underpin the development of novel and improved bacterial vaccines. We still don't understand how the human immune system responds to or interacts with certain pathogens. Animal models have proven somewhat useful, but the interpretations are not readily translatable, especially when the pathogen is host-specific. For example, *N. meningitidis* only infects humans. While we do have some tools that have certain components of the human immune system, such as humanized mice, they don't represent a complete solution.

There is also a significant knowledge gap in the area of correlates of protection. This is critical because, for certain diseases, large-scale vaccine efficacy trials are not feasible prior to roll-out. In these cases, we rely on *in vitro* surrogates of protection to determine if the vaccine will be useful in humans. We are fortunate in the field of meningococcal disease research in that we have a fantastic and robust surrogate of protection—the serum bactericidal assay. But for many other pathogens, the development, standardization, and optimization of correlates of protection remains a significant challenge (putting it in mild terms), despite significant ongoing efforts. A lack of understanding of what constitutes the system of protection against certain pathogens (i.e., antibody induction, cell-mediated, complement activation, etc.) contributes to the inability to develop relevant *in vitro* surrogates of protection.

A further aspect is our lack of understanding of what actually makes a protein immunogenic. What makes an epitope functionally immunogenic versus not functionally immunogenic? That's still another key question that we have yet to answer. If we could answer this, most likely using advanced structural biology techniques plus computational modelling, then we'll be a lot closer to identifying vaccine constituents that will not only evoke the robust protective response we desire but also limit the negative off-target effects that may arise from unintended immune activation or imbalances. This would be a major step toward creating safer, more effective vaccines that not only deliver the robust protection we aim for but also minimize unintended adverse effects.

Q How does your approach differ to traditional vaccine development?

FB My current research cuts across all of the stages of the preclinical vaccine development process—discovery, design, and delivery.

To understand the foundational approach we are employing (at the discovery stage)—Reverse Vaccinology 2.0 or RV 2.0—we need to first consider Reverse Vaccinology 1.0, also known as classical reverse vaccinology (classical RV). In classical RV, you start from the

"The advantage of [Reverse Vaccinology 2.0] is that it allows us to bypass animal model studies by leveraging existing human data (functional activity of the cloned fully-human antibodies)."

whole genome sequence of the pathogen. Putative surface-expressed proteins are identified using bioinformatic tools, and then recombinantly expressed. Next, these expressed proteins are used to immunize rodents or other suitable animal models for induction of antibodies. Induced antibodies are then tested in the lab for functional activity to identify potential vaccine candidates. Candidates are progressed through to Phase 1 clinical trials to determine safety and immunogenicity in humans. However, some of the vaccine candidates that have been successfully confirmed to be immunogenic in animals, may not prove to be immunogenic in humans.

With RV 2.0, classical RV is reversed, essentially starting where classical RV 'ends' i.e., identifying antibodies that are functional in humans, before working out to what protein in the pathogen those antibodies bind. My team does this by approaching individuals recovering from a target disease, cloning antibodies from those individuals and assessing the functional activity of these cloned antibodies. We then use classical immunoproteomics, protein arrays, and epitope fingerprinting to identify the specific epitope (and antigen it composes) that induced the production of the antibodies in humans (our recovering patients). The advantage of this approach is that it allows us to bypass animal model studies by leveraging existing human data (functional activity of the cloned fully-human antibodies).

Q How can this data be presented to regulators in a way that they will deem suitable?

FB I believe the RV 2.0 community will first need to build momentum and coordinate efforts across groups. This is essential—I cannot stress this enough. We will also need to involve advocates of 'the 3Rs' ethical principles of animal studies—replacement, refinement, and reduction.

This has been a hot topic of conversation at recent conferences I have attended—the need to have regulators in the room when we are having these discussions is beginning to come to the fore and I am hopeful that in the next year or two, we will be able to open these discussions with European regulators so that when we reach the clinical trial application stage with our vaccine candidates, there will be fewer hurdles to address.

Q What are some important high-throughput tools that you are using?

FB I think the definition of what constitutes 'high-throughput' is becoming a bit more fluid. I would suggest that the concept of RV 2.0 actually qualifies as high-throughput, because it allows rapid progress towards desired outcomes.

Consider the previous vaccine antigen discovery methods, which were mostly hypothesis-based—for example, my 4-year PhD project. At the end of those 4 years, we learned that the antigens I was working on were unlikely to be viable vaccine candidates. That essentially represents 4 years of time, money, and labor that didn't lead to the desired outcome. Through the RV 2.0 method, however, we have identified multiple viable and novel targets within a similar timeframe (which is non-inferior to the pace with which classical RV generated viable antigens). The advantage is that a single lab gains the capability to identify as many novel candidates as multiple labs can, within the same or even shorter time frame.

Turning to high-throughput tools in the more conventional sense, we collaborated with Antigen Discovery, Inc. in California to develop a meningococcal multiproteome protein array. This meningococcal array allowed us to screen hundreds of our RV 2.0-derived antibodies against approximately 1,000 meningococcal proteins, yielding exciting unequivocal targets of our most promising antibodies. There is scope for scale-up of these arrays to 2,000–5,000 proteins, or even more, to ensure greater coverage of circulating variants of important membrane proteins.

We are also advancing in the development of high-throughput antibody cloning tools. We published a method in 2023 that allows the isolation of pathogen-specific antibody-producing B cells using whole, inactivated bacterial cells [2]. This was a first for the field. Prior to that, vast antibody libraries were cloned, only a small fraction of which would target an epitope expressed by the pathogen of interest. Single proteins enabled the isolation of specific antibody-producing cells but this approach, while suited to qualitative assessments of the immune response to vaccination, is not useful when the goal is to discover novel antigens, as it relies on pre-identified proteins rather than uncovering new targets.

Q Can you expand on how you have applied these techniques so far?

FB To date, in our lab, we have mainly applied the techniques with *N. meningitidis*, *S. pneumoniae*, and *N. gonorrhoeae*. Although they cause very different diseases, *N. meningitidis* and *N. gonorrhoeae* are very close cousins that share a lot of surface proteins, and we believe there is much to be learned from applying the techniques across the two.

In terms of the key findings, we are now at the stage of having identified not just the protein, but the specific epitope that has induced functional antibodies in patients. This is a major advancement for both the meningococcal and pneumococcal fields. We are in the final stages of putting the manuscripts together and hope that they will be published in the first quarter of 2025 or shortly thereafter.

In fact, these findings are so key that we are now going through the process of securing intellectual property rights with Imperial College London. This prevents me from going into much detail here, but one intriguing (and equally exciting) finding relates to the subcellular localization of the discovered antigens and epitopes. Due to their topology, these antigens would have naturally been missed using previous approaches, which further lends credence to the RV 2.0 approach. We have clearly not been privy to a lot of the interactions between the human immune system and the pathogen, and we hope our approach will uncover many exciting new findings.

Q Can you go deeper on why *N. meningitidis*, *S. pneumoniae*, and *N. gonorrhoeae* were initially targetted?

FB My work with *N. meningitidis* goes a long way back. One of the reasons why I chose *N. meningitidis* in the first place was the ease of working with it. It is a Gram-negative pathogen that is easy to culture, and easy to work with in many different aspects, once safety considerations have been adequately addressed (it can kill in under 24 hours, so appropriate protocols must be in place to mitigate risks).

Of course, the importance of the diseases that *N. meningitidis* causes was a further key factor in selecting it. I have something of a love–hate relationship with *N. meningitidis*—as much as I love the bacterium scientifically speaking, I would equally love to be one of those who will eventually eradicate it from the face of the earth.

When I transitioned to focusing on RV 2.0, *S. pneumoniae* was a natural progression because it is also a chief cause of bacterial meningitis and septicemia, in addition to pneumonia (the leading infectious cause of mortality in children). The decision to extend our application of RV 2.0 to *N. gonorrhoeae* first stemmed from data that demonstrated reactivity of our panel of anti-meningococcal hmAbs with gonococcal surface proteins—unsurprising, given the close relatedness of both pathogens. Furthermore, since the preferred product characteristics of prospective meningococcal vaccines is protection against gonococcal disease (50–55% protection over a 6-year period could yield a 90% reduction in disease incidence [3]), there is a potential to develop a combination vaccine that would protect against both meningococcal and gonococcal diseases, and RV 2.0 could be utilized for antigen discovery.

The importance of the concept of combination vaccines relates to vaccine uptake today, especially in the context of pediatric infectious diseases, with parents being increasingly concerned about the number of vaccines and doses that their children receive. In a recent survey of parents, one of the key pieces of feedback was a request to reduce or condense the immunization schedule (expressed at a recent webinar on New Combination Vaccines sponsored by the Bill and Melinda Gates Foundation, July 30, 2024). The idea of being able to protect against 5 or 6 pathogens through a single administration is one of the key goals of the work that I am doing currently. My lab is focusing mainly on combination vaccines and if we can develop a combination that can offer long-term protection against meningococcal, pneumococcal, and gonococcal disease at the same time, that would be a fantastic achievement.

Our work extends to other pathogens, especially those of global economic significance in antimicrobial resistance. *N. gonorrhoeae* represents our first foray into this critical antimicrobial space, while pathogens like *Klebsiella pneumoniae* are also on our radar for future exploration.

Q How confident are you that potential vaccine targets identified through convalescent patient samples will translate to the target populations?

FB That's a very good question. In terms of age, all our convalescent patients for meningococcal and pneumococcal diseases were children, which reflected the

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target population. In fact, the very first meningococcal disease patient we worked with was a 9-month-old infant, unfortunately. That case showed that we could apply the RV 2.0 approach to pediatric patient samples.

Of course, with respect to gonococcal disease, all the patients we work with are adults. There, our focus is not on the age-related appropriateness of the vaccines but on their global appropriateness. Because the genetic epidemiology of gonococcal strains differs across geographical regions of the world, it follows that convalescent patient samples from the Eastern and Southern regions of Africa, where the burden of disease is highest, should be a major subject of our gonococcal RV 2.0 study. This will ensure heightened relevance of a prospective vaccine identified from our studies.

Q What other recent advances have you seen in the immunology field that give you hope for the future? What was the most exciting paper you read in 2024?

FB It would have to be AI and advances in the computational field in general. We are gaining access to some fantastic software now, one example of which is AlphaFold, which replicates some of the data we are generating in the lab.

Of course, the utility of AI is dependent on the quality of training data, and there is yet a significant amount of wet lab work needed to generate this data. I don't see us becoming completely dependent on AI tools, but they can and will be a fantastic partner in vaccine discovery. I'm really excited about that, and it's an area in which we are working hard. My group is interested in collaborating with those in the AI field with the goal of creating an AI-based RV 2.0 approach (Reverse Vaccinology 3.0?).

The most exciting paper I have read recently (currently in press) goes back to my earlier comments about what makes an immunogenic protein either useful or useless. The paper shed light on expressing a vaccine antigen in different cellular backgrounds (insect versus Chinese hamster ovary cell lines) and how the different glycosylation patterns in these backgrounds affected functional immunogenicity. The relevance of this paper lies in its demonstration that during the mass production of vaccine antigens in industry, the choice of cell line used to express and produce a vaccine antigen is critical. It highlighted that different cell lines can result in varying decorations of the antigen, which can ultimately determine the effectiveness of the vaccine in humans.

Q Finally, what future developments in tools and technology would be most valuable to your research?

FB AI again—particularly in the context of looking for correlates of protection to accelerate the vaccine development and licensure processes. I would also add human challenge studies, which are becoming increasingly important as we develop protocols to help ensure the safety of volunteers during these studies.

REFERENCES

1. Ladhani SN, Andrews N, Parikh SR, *et al.* Vaccination of infants with meningococcal group B vaccine (4CMenB) in England. *N. Engl. J. Med.* 2023; 382, 309–317.
2. Siris S, Gladstone CA, Guo Y, *et al.* Increasing human monoclonal antibody cloning efficiency with a whole-cell modified immunoglobulin-capture assay (mICA). *Front. Immunol.* 2023; 14, 1184510.
3. Whittles LK, White PJ, Didelot X. Assessment of the potential of vaccination to combat antibiotic resistance in gonorrhea: a modeling analysis to determine preferred product characteristics. *Clin. Infect. Dis.* 2020; 71(8), 1912–1919.

BIOGRAPHY

Fadil Bidmos was born in Lagos, Nigeria and completed his education up until his undergraduate degree there (BSc Cell Biology and Genetics at University of Lagos, Lagos, Nigeria). After studying the potential effect of phase variation on long-term asymptomatic colonization of the human nasopharynx by the meningococcus, he obtained a PhD in meningococcal genetics and immunology, with specific focus on the vaccine candidacy of the phase variable iron-acquisition proteins, HpuAB and HmbR. A 5-year stint as a postdoctoral fellow in the Langford Lab at Imperial College London, London, UK followed—here, he used the Reverse Vaccinology 2.0 (RV 2.0) strategy to discover novel meningococcal and pneumococcal vaccine antigens. Funding, gratefully received, from the UK Medical Research Council (Career Development Award: 2019–2024; and Senior Non-Clinical Fellowship: 2024–2029) enables his research, which also includes innovative use of bacterial and synthetic cell glycoengineering for enhanced vaccine precision and effectiveness. His budding lab has also received funding for efforts to apply RV 2.0 to gonococcal vaccine antigen discovery and alternative post-infection therapeutics (NIHR Imperial BRC) and development of a meningococcal panproteome array (collaboration with Antigen Discovery Inc., USA—NIH SBIR Phase 1). He has a strong commitment to education, supporting both undergraduate and postgraduate students at Imperial College London and other prestigious institutions worldwide. In recognition of his teaching standards, he was awarded Fellowship of the UK Higher Education Academy (FHEA) in 2016. Additionally, his management and leadership skills were acknowledged with the Chartered Fellowship (FCMI CMgr) of the UK Chartered Management Institute in 2023. He also contributes to the wider scientific community in several capacities including as an External Editor for Springer Nature's *Communications Medicine* journal and membership of working groups assessing the impact of vaccines on antimicrobial-resistant pathogens.

Fadil Bidmos, UK MRC Senior (Non-Clinical) Fellow and Proleptic Senior Lecturer in Bacterial Vaccinology, Department of Infectious Disease, Imperial College London, London, UK

AUTHORSHIP & CONFLICT OF INTEREST

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THE BIG QUESTION

Seven unresolved questions for vaccine science in 2025

What is the greatest unresolved question in vaccine science today? Members of the *Vaccine Insights* expert editorial advisory board share their burning questions, and explain why answering them is crucial to the future of the field.

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What will a broadly effective HIV vaccine look like?

Jeffrey Ulmer How to solve the so far intractable problem of developing a broadly effective HIV vaccine. Progress has been made but a solution has proven to be elusive.

A promising, but very daunting, strategy is to target receptors on naive germline B cells and entrain them to produce broadly neutralizing antibodies. This may require structure-based design of HIV antigens and a careful sequence of vaccinations to drive appropriate affinity maturation.

Jeffrey Ulmer PhD is President of TechImmune LLC

What exactly is the relationship between composition and safety?

Ingrid Kromann Artificial intelligence has emerged as a powerful tool in understanding complex relationships in vaccine development, particularly in assessing the impact of composition—including host cell proteins (HCPs) and impurities—on vaccine safety. I hope AI can help to provide more precise answers, and to minimize the number of animals used in not-very-specific toxicology studies.

Ingrid Kromann is Senior Advisor, Manufacturing and Supply Chain at CEPI

Can we identify new correlates of protection?

Marco Cavaleri The use of immune markers as correlates of protection, or at least as suitable surrogate endpoints that are likely to predict protection.

Despite efforts in understanding immunological responses to vaccines and which type of responses drive protection by vaccines, there are still major gaps and difficulties in identifying immune markers that can be measured by standardized assays. Especially for cellular-mediated immunity, it has been so far impossible to utilize any specific immune parameter as an agreed correlate of protection. Deeper understanding of protection, not only in the short term but also in the longer term, is necessary to better predict the need for booster doses and ability of vaccines to confer long-lasting protection.

Lastly, mucosal immunity has been associated with significant measurement challenges, limiting the use of such important immunological information when defining correlates of protection.

Marco Cavaleri is Head of Health Threats and Vaccines Strategy at EMA

What is the future of vaccine clinical trial design?

Cristiana Campa How to properly design clinical trials to drive rapid and reliable vaccine development, and support product quality understanding.

To address the question, continued exploration of nonclinical tools (aiding prediction of safety and efficacy), re-use of information from similar vaccines/ platforms, and model-informed vaccine development could play a critical role.

Cristiana Campa PhD is CMC External Intelligence Lead, Vaccines Technical R&D at GSK

Can we develop better adjuvants?

Denny Kraichely While I considered other aspects like the need to maintain cold-chain (not unique to vaccines) and conventional challenges like host and pathogen variability, I believe that the greatest unresolved question is the development of safe and potent immunologic adjuvants that can increase and direct vaccine-specific immunity.

While extremely important, research on vaccine adjuvants has received little attention from the main research funding agencies and policy makers. Adjuvant development needs more attention, focus, and investment.

Denny Kraichely PhD is Global Program Leader, Vaccine Development Management at Pfizer

Can newfound knowledge on vaccine-induced immunity improve the durability of protection?

Christopher Ton Some vaccines provide lifelong immunity with a single dose, while others only provide limited protection following boosters. To date, most vaccines have been developed empirically, and we still have very limited knowledge of vaccine mechanisms and their interactions with innate and adaptive immune systems.

Recent advances in analytical methods to characterize and quantify T cells response can help to narrow our knowledge gaps of vaccine-induced immunity. In addition, novel adjuvants and antigen delivery methods can help to improve vaccine durability.

Christopher Ton PhD is Principle Scientist, Vaccines & Advanced Biotechnologies Process Development at Merck & Co

How can we boost the durability of mRNA-LNP vaccines?

Ana Jacklenec Improving vaccine durability, particularly for mRNA-based vaccines, to ensure that a single dose provides robust and long-lasting protection.

A potential solution involves encapsulating mRNA lipid nanoparticles (LNPs) in controlled-release systems such as SEAL [1], enabling the delivery and release of the vaccine over weeks or months to extend its durability. Achieving this requires stabilizing mRNA-LNP formulations to withstand body temperature and environmental conditions.

Strategies such as immobilizing mRNA-LNPs in a solid matrix and using excipients to prevent oxidative degradation can improve the stability of current mRNA-LNP vaccines, which are inherently unstable and degrade rapidly in vivo.

Emerging tools like advanced bioinformatics, high-throughput screening, and self-amplifying mRNA technologies are aiding the development of next-generation mRNA vaccines by optimizing mRNA sequences, enhancing LNP stability, and supporting prolonged antigen expression.

Additionally, innovations in nanotechnology and synthetic chemistry are driving the creation of advanced LNPs with enhanced durability and immunogenicity. Overcoming these challenges will improve vaccine accessibility and support global immunization efforts.

1. McHugh KJ, Nguyen TD, Linehan AR, et al. Fabrication of fillable microparticles and other complex 3D microstructures. *Science* 2017; 357(6356), 1138–1142.

Ana Jaklenec PhD is Principal Investigator, Massachusetts Institute of Technology at the David H Koch Institute for Integrative Cancer Research

BIOGRAPHIES

Jeffrey B Ulmer spent more than 30 years in vaccines R&D at Merck Research Laboratories, Chiron Corporation, Novartis, and GlaxoSmithKline. His most recent leadership positions included Global Head, External R&D; Head, Preclinical R&D; and Program Head, Technical R&D. His scientific focus has been vaccine technology platforms, including DNA and mRNA vaccines, viral vectors, and adjuvants. He received his PhD in biochemistry from McGill University, Montreal, QC, Canada and completed his postdoctoral training in the laboratory of Nobel laureate Dr George Palade in the Department of Cell Biology at Yale University School of Medicine, New Haven, CT, USA. He has published over 210 scientific articles, is an inventor on 11 patents, and is a Fellow of the International Society for Vaccines where he serves as Deputy Chair, Executive Board. He is currently President, TechImmune LLC (Newport Beach, CA).

Ingrid Kromann started on March 1, 2020 as Head of CMC, CEPI, London, UK, and from January 2022 as Acting Executive Director of Manufacturing & Supply Chain Division. The CEPI Manufacturing & Supply Chain Division is supporting the vaccine development projects, implement new innovative technologies and, establish sustainable

development-manufacturing facility- and supply chain networks to rapidly deliver equitable vaccine access where and when needed. Ingrid has a background as chemical engineer. She has more than 25 years of experience of working with vaccines through her employment at Statens Serum Institut, Denmark. For the last 16 years, Ingrid led the vaccine development department at Statens Serum Institut, and has developed more than 10 different vaccines from research to clinical trials, mostly within tuberculosis, polio and chlamydia.

Marco Cavaleri is the Chair of EMA COVID-19 Task Force (ETF) and responsible for EMA activities for emergent pathogens, vaccines, and antimicrobial resistance. Marco is a pharmacologist who spent several years in industry research and development, mainly in preclinical and clinical development of anti-infectives. In 2005, he joined the EMA as Scientific Administrator in the Scientific Advice Sector, specifically anti-infectives and vaccines scientific advice procedures, and in 2009 he was appointed as Head of Section for Anti-infectives and Vaccines in the Safety & Efficacy Sector, Human Medicines Development and Evaluation Unit.

Cristiana Campa has more than 20 years' experience in Chemistry, Manufacturing and Control (CMC) for biologics research and development. She is actively promoting dialogue across industry and with Regulatory Agencies on several topics, including innovative technologies, specifications setting, stability, accelerated development strategies, and pandemic preparedness. Since 2023, she is a member of the PDA Board of Directors, and, since 2024, she is the EFPIA lead in the ICH Expert Working Group for ICH Q6 (specifications) Guideline revision, co-chair of the PDA Vaccine Interest Group, and chair of the Vaccines Europe/IFPMA CMC Adaptive Pathways team (former COVAX support team).

After her PhD and Post-Doc in Chemistry, Cristiana worked at Bracco Imaging SpA, first as a senior researcher and then as head of the research laboratory in Trieste, Italy. She joined Novartis Vaccines in 2006, first as Analytical Senior Manager and subsequently as Head of Analytical Development, Italy. After acquisition of Novartis Vaccines by GSK in 2015, she has been the Head of Quality by Design Integration and, until June 2018, the Head of Science and Development Practices in Global Technical R&D, covering Quality by Design, Knowledge Management and Development roadmaps; until February 2025, she worked as a Global Vaccines Technical R&D Advisor, GSK.

Denny Kraichely is an accomplished scientist, author, and inventor. After receiving a PhD in Pharmacological and Physiological Science from Saint Louis University, St. Louis, MO, USA he completed a short post-doctoral fellowship, then joined the pharmaceutical industry. Over the past 20+ years, through strong technical expertise and cross-functional matrix leadership of internal and cross-company teams, his efforts have contributed to the development and approval of multiple biologic therapeutics and vaccines. In his current role at Pfizer, he manages and guides vaccine research and development program teams to develop aggressive, forward-thinking development plans that maximize scientific, medical, and commercial value.

Christopher Ton has over 23 years of experience in the life science industry, including process development, optimization, scale-up, tech transfer and GMP manufacture of cell therapeutics, and live viral vaccines. He received his PhD in Molecular Biology from the University of Toronto, Toronto, ON, Canada. Since joining Merck in 2009, his primary focus has been on vaccine upstream bioprocess development. He has led and contributed to the development of multiple vaccine candidates such as SARS-CoV-2 and dengue vaccines.

Ana Jaklenec has over 15 years of experience in bioengineering, materials science, micronutrient and vaccine stabilization and delivery. She has published over 100 manuscripts, patents, and patent applications and has founded three companies: Particles for Humanity, VitaKey, and OmniPulse Biosciences. Her major focus is the study and development of polymers to deliver liable drugs, particularly vaccines, DNA vectors and mRNAs, in stable form for prolonged periods of time with unique kinetics. Her lab is currently working in the following areas: developing single-injection self-boosting vaccines; nanocarrier-based vaccine approaches targeting protective memory responses after parenteral immunization; 3D printed on-demand microneedle vaccines; developing on patient medical records using invisible dyes; creating long-term drug delivery systems for cancer immunotherapy; developing heat stable polymer-based carriers for oral delivery of micronutrients and probiotics. Dr Jaklenec is the recipient of the Ruth L Kirschstein National Research Service Award (NRSA) from the National Institutes of Health (NIH) and was elected to the National Academy of Inventors (NAI) 2023 Class of Fellows, the highest professional distinction for academic inventors in the United States.

AUTHORSHIP & CONFLICT OF INTEREST

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