Vaccine Strategy: Ab Osterhaus

A new route to pandemic preparedness

In late June, the international medical journal *Vaccines* published Phase 1 clinical data about a new vaccine platform that is being positioned as a technology to prepare for future pandemics[1]. The platform is being developed by AdJane Holding BV of the Netherlands and is based on 30 years of government funded research with the goal of discovering whether mucosal immunity – where the body's own antibodies neutralise pathogens before they enter tissues – has potential as a more widely exploited future vaccination strategy.

The study, carried out in 40 healthy adults, paired the company's native outer membrane vesicle (nOMV) platform with a SARS-CoV-2 spike protein – a structural component of the virus that caused the COVID-19 pandemic. It was delivered via a mucosa targeting platform, where delivery is through the body's mucous membranes, rather than by injection. The results showed that the vaccine is safe and well tolerated and produced a dose-dependent systemic and mucosal immune response. This included generating virus neutralising antibodies and a virus specific immunoglobulin A (IgA) response at the nasal mucosa. This is the entry point for most respiratory pathogens. The study was among the first published human readouts for an OMV vaccine given by this route.

OMVs are naturally occurring, nano-sized particles released by Gram-negative bacteria at times of stress. They may regulate a host immune response by activating the innate immune system or contribute to the resistance of bacteria to antibiotics. The technology was first observed on electron microscopy in the 1960s. Two decades later, it was used to develop outbreak-control vaccines against serogroup B meningococcal disease, including Cuba's VA-MENGOC-BC and Norway's MenBvac in the 1980s and 1990s. An OMV component was later incorporated into Bexsero, developed by GSK Plc to prevent serogroup B meningococcal disease more broadly. The US Food and Drug Administration approved Bexsero in 2015 and in 2024, it updated the dosing schedule. Most recently, on 20 July, GSK asked to have the dosing schedule also updated in Europe.

The pandemic challenge

For decades, global health authorities have talked about the importance of platform diversity in the context of pandemic preparedness. The severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks highlighted the same weaknesses in the global healthcare response twice – a decade apart.

SARS spread in Hong Kong and through hospital wards in Toronto, Canada in 2002–2003 before any vaccine platform was ready. The outbreak was eventually contained by non-pharmaceutical intervention measures. This prompted the World Health Organization to rewrite the International Health Regulations in 2005 and force faster outbreak reporting.

A decade later, a single traveller returning from Saudi Arabia to South Korea in 2015 and infected with MERS coronavirus caused the start of an outbreak affecting roughly 180 cases, mainly through hospital transmission. This was a sign that the lessons from SARS had not been fully learned. The 2009 H1N1 influenza pandemic underscored a different vulnerability: vaccine manufacturing couldn't scale fast enough to deliver the required products. In this latter scenario, wealthy countries bought up limited early supply, and because the virus caused a milder disease than expected, preparedness funding lapsed once the crisis passed.

COVID-19 repeated these limited preparedness patterns with much more severe consequences, contributing to an estimated 15 to 20 million deaths globally. Some lessons did stick: the speed of the messenger RNA vaccine development owed a great deal to US National Institutes of Health-funded structural vaccinology work on stabilised spike proteins that began after MERS. But one important gap was visible as early as SARS and never closed: none of the major platforms used efficiently delivered mucosal immunity. This is a potential first line of defence at a point where respiratory viruses enter the human body.

Pandemic preparedness plans drawn up in ordinary times are familiar to those who work in public health and vaccinology. They include securing hospital capacity, early warning systems, pathogen discovery platforms, linked diagnostic and clinical trial infrastructure, and biosafety level 3 facilities. These are among the non-pharmaceutical interventions that are available before pathogen-specific tools exist. But though the playbook is familiar, the tools are far from failsafe to face a major pandemic.

Among the frontline pharmaceutical tools, targeted vaccines and antivirals remain the most effective way to limit severe disease, transmission, and broader disruption. But because universal vaccines against pandemic-potential virus families don't yet exist, new vaccines must be developed fast once a pathogen is identified. This is why, during Covid-19, the platforms that succeeded best were the modular ones. They included mRNA, viral vector, and recombinant protein based vaccines which let developers swap in a new target antigen rather than start from scratch. This 'plug-and-play' approach helped when SARS-CoV-2 itself began to mutate during the recent pandemic.

What none of these platforms solved however was the efficient induction of mucosal immunity. Injectable vaccines struggle to generate strong immunity at the nasal and airway surfaces where respiratory viruses first take hold. This is a response that can help prevent or stop the infection at an early stage, forestalling severe disease and probably reducing virus transmission. Currently, several initiatives are aimed at developing candidate pandemic vaccines that also induce mucosal immunity. These include mRNA, viral vector, and adjuvanted recombinant protein vaccines. In their current forms however, they are poorly

suited to intranasal delivery without major reformulation or unacceptable local reactogenicity. This leaves a hole in the pandemic preparedness toolkit which, during the Covid-19 pandemic, was clearly identified as an important point to consider.

As discussed earlier, an OMV component became part of GSK's licensed Bexsero vaccine. OMVs carry outer membrane proteins, lipopolysaccharide (LPS), and lipoproteins in their native conformation, closely resembling what the immune system meets during a real infection. That makes them inherently immunogenic and self-adjuvanting. Their pathogen-associated molecular patterns (PAMPs) activate immune responses without needing a separate adjuvant, and their small particulate size (20–300 nm) contributes to uptake by mucosal antigen-presenting cells and secretory IgA production, the antibody class that neutralises pathogens right at the point of entry.

What the initial OMV vaccines couldn't do was scale up beyond the strain from which they came. Protection was driven largely by strain-specific surface proteins, so a vaccine built from one outbreak strain offered little protection against another. This is useful for controlling a local epidemic, but less helpful as a general-purpose platform.

Three further challenges compounded this. Native LPS is potent enough to cause real local and systemic reactions at the doses needed for good immunogenicity; wild-type bacteria shed usable vesicles too inefficiently to manufacture at scale; and attaching a foreign antigen to the vesicle surface tends to either destabilise the vesicle or blunt the PAMP activity that makes OMVs self-adjuvanting in the first place. The four interconnected barriers of reactogenicity, yield, strain specificity, and antigen display, hold back a platform with a long history and clinical track record, from becoming a general epidemic- and pandemic-response technology.

What AdJane's technology has done is to fill a gap in the pandemic preparedness toolkit: induction of mucosal immunity. In the words of the company's chief executive, Anita Gashi, it has addressed the historical barriers to broader OMV use which include reactogenicity, yield, strain specificity, and manufacturability, to potentially bring the technology to bear across a broad range of viral and bacterial threats. This enables the company to respond to global health challenges as they evolve.

The company's *Neisseria meningitidis* – native OMV backbone addresses many of the setbacks which have held back the OMV platform. It uses a genetically engineered *N. meningitidis* strain carrying four targeted gene knockouts, each aimed at one of the four historical barriers: reducing reactogenicity, improving spontaneous vesicle yield, limiting strain-specific immune interference, and supporting stable display of heterologous antigens. The data published in *Vaccines* provides the first human evidence and the first time this line of engineering has been tested against a pathogen with genuine pandemic potential rather than a single outbreak strain.

The fact that this version of the OMV platform can be given intranasally is a potential gamechanger for pandemic preparedness. This is the first time the OMV platform has been engineered to be administered mucosally in humans, providing an important differentiator against competing technologies. The possibility for using it also for seasonal vaccines against continuously mutating respiratory viruses, such as SARS-CoV-2 and influenza viruses, would offer the additional opportunity of routinely using it for seasonal vaccination of high-risk groups by using the 'plug-and-play' strategy. This could also be used directly for a pandemic vaccine, once the pandemic virus has been identified. This approach would be important from a sustainability perspective as using a platform technology for pandemic preparedness only, rather than using it routinely for seasonal vaccine production, would not be attractive or feasible from a financial point of view.

Alongside the major platforms that were used for the development of the Covid-19 vaccines, OMVs occupy a distinct segment. Current mRNA vaccines largely depend on the use of lipid nanoparticles and are poorly suited to mucosal delivery. Viral vectors lose potency with repeated dosing as anti-vector immunity builds. Conventional adjuvanted vaccines mainly drive systemic immune responses. They usually don't work intranasally at the dose range used for parenteral administration. AdJane's OMVs, by contrast, are self-adjuvanting, can be given either parenterally or intranasally allowing both mucosal and systemic immunity induction. This is a combination none of the platforms that dominated the response to the last pandemic could offer.

In April, the global non-profit partnership, CARB-X, awarded AdJane $2.6 million to advance a gonorrhoea vaccine candidate using the same native OMV backbone as in the company's candidate pandemic vaccine to address antimicrobial resistance. Taken together with the June trial data, the two programmes point to one underlying technology which could be positioned for pandemic preparedness and preventing seasonal respiratory and bacterial infections, both with an impact on the reduction of antimicrobial resistance. This breadth of application is important because pandemic preparedness increasingly depends on having several distinct platforms ready to adapt, not one dominant technology which has been scaled up 'after the horse has bolted.'

The removal of these initial stumbling blocks has enabled OMV to mature as a vaccine development platform for mucosal and parenteral application. This has enabled it to produce its first published human data against a seasonal – and pandemic-relevant – pathogen. For a platform that has spent decades solving one barrier at a time, this offers intriguing opportunities for vaccine developers.

Reference:

1. Kraan, H., van der Geest, A., Oosterhoff, D., Kruiswijk, C., et al. (2026). A Randomized, Double-Blind, Placebo-Controlled Phase I Study to Evaluate the Safety, Tolerability, and Immunogenicity of an Outer Membrane Vesicle (OMV) Platform-Based Vaccine Administered Intranasally to Healthy Adults. *Vaccines*, 14(7), 575.

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