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Who Needs Next Gen Vax Tech?

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The COVID-19 vaccines were developed in record time. As the 'novel' coronavirus mutates, the vaccine makers, too, are adapting by innovating vaccine technologies. Researchers continue to work, aiming for more potent immunity, reduced transmissibility, cheaper manufacturing, easier transport, and mutation-targeted vaccines. The novel vaccine models may facilitate rapid and effective responses to new infectious diseases, allergies, autoimmune conditions, and cancers. Vaccination programmes can be more cost-effective and efficient by achieving global outreach, maintaining vaccine potency, and optimising logistics, thus increasing global preparedness for future pandemics and disease outbreaks. Let's explore some of the latest advancements in vaccine technology which emerged in the era of COVID-19.



Globally, mass vaccination practices and procedures were not pleasant experiences for everyone. Different age groups and vulnerable populations had to undergo mandatory national vaccination procedures to access the essentials in public spaces. Additionally, minimising injection discomfort and biohazards from syringe disposal are also serious concerns. The aim of innovative vaccines is to achieve multi-target vaccines to eliminate the need for multiple-bolus regimens. Being compliant to both manufacturer and consumer could be a potential solution for high-impact mass vaccination.

While expenses on vaccine manufacture/delivery/storage/supply chain have become a burden on a nation's economy, the World Health Organisation (WHO) is acknowledging the idea of a single-injection vaccine, as a preferred immunisation method. Novel injection-free and single-dose medication and vaccine delivery strategies are a pressing need of the moment. There are different ways of delivery of drugs and vaccines and some of the latest trends include Nanosystems for Transdermal Delivery, Nasal sprays, Dissolvable microneedles etc.

Nanosystems for Transdermal delivery

Nanosystems comprising nanoparticles and liposomes can effectively transport antigens within parenteral (intravenous) administration. Majority of COVID-19 mRNA vaccines under clinical development are designed to deliver by lipid

nanoparticles (LNP). Immunity triggering viral antigens can be incorporated into the nanoparticles via encapsulation or by conjugation to prolong the stability of mRNA by preventing its degradation.

Similarly, nanotechnology can also enhance immunogenicity and stability of ‘soluble protein antigens’ combined with adjuvants. Targeted delivery reduces antigen in a dose, which is helpful when striving for mass vaccination.

The co-delivery of nanoparticle-based vaccines with adjuvants can greatly enhance vaccine potency. The versatility of nanoparticle systems makes them suitable for delivering vaccines against other emerging pathogens. Vaccine adjuvants reduce vaccine cost, improve antigen immunogenicity, and increase antigen stability.

Novel all-in-one vaccine for multi variant virus

In July 2022, Coalition for Epidemic Preparedness Innovations (CEPI) announced up to $30 million in funding to the University of Oxford to develop nanoparticle vaccines offering protection against a range of coronaviruses. In contrast to many existing vaccine designs that use mRNA or a viral vector to present sections of the spike protein of a single type of virus to the immune system, this new vaccine will use protein nanoparticles containing a protein ‘glue’ to attach related antigenic sections of the spike proteins from eight different viruses. By incorporating a ‘mosaic-8 vaccine’ design created at Caltech these nanoparticles would favour immune responses to the shared parts of each of the different types of coronaviruses within a single vaccine.

“The “glue” for sticking proteins together was developed by Dr Mark Howarth of Biochemistry, Oxford. Together we used this technology to make a prototype nanoparticle SARS-CoV-2 vaccine that induced highly potent responses in preclinical studies. We made a fully functional version of the vaccine produced in microbes, thus reducing the cost of production” said **Alain Townsend, Oxford Lead of the consortium, Professor of Molecular Immunology at the MRC Weatherall Institute of Molecular Medicine, University of Oxford**.

Dr Jack Tan, Project Manager (Oxford) of the consortium, Senior Postdoctoral Scientist at the MRC Weatherall Institute of Molecular Medicine, said, “CEPI to further this nanoparticle technology with the goal of producing efficacious, low-cost, infrastructure-independent vaccine that will be accessible to low- and middle-income countries.”

Nasal sprays and Aerosol vaccines

Nasal vaccines: Vaccines are usually administered intramuscularly, subcutaneously, or intradermally using hypodermic needles. Nasal vaccines, jet injectors, microneedles, and nanopatches are arriving as a potential painless and cost-effective approach to vaccination while avoiding expensive coldÃ¢â?¬Âchain transport and storage.

The prospects of nasal vaccines are seemingly optimistic for COVID-19 which can further lay the foundation for noninvasive vaccine delivery modes. Intranasal needle-free vaccines are easier to distribute among low income countries lacking healthcare aid. They can elicit both mucosal and systemic immune responses releasing immunoglobulins, mucosal IgA, and serum IgG, similar to a SARS-CoV-2 infection and thus the nasal route is seen as a promising vaccine strategy. Intranasal flu vaccines, such as FluMist, were introduced to the US market in 2003.

“If the infectious disease attacks the respiratory tract then you need respiratory mucosal immunity. In such case aerosolised vaccine could be beneficial,” explains **Aurelio Bonavia from the vaccine development group at Bill & Melinda Gates Medical Research Institute**.

In early September 2022, India’s first intra-nasal COVID-19 vaccine iNCOVACC (BBV154) by Bharat Biotech received Emergency Use Authorisation (EUA). With the approval in India, it thus became the second needle-free intranasal vaccine to clear regulatory approval after China’s CanSino Biologics’ vaccine. Approximately, 100 similar nasal vaccines are under development for Influenza and Covid-19 across the world concerning low- and middle-income countries.

"Bharat Biotech's ChAd36-SARS-CoV-S COVID-19 recombinant nasal vaccine approved by @CDSCO_INDIA_INF for primary immunisation against Covid-19 in 18+ age group for restricted use in emergency situation," tweeted **Health Minister of India, Dr Mansukh Mandaviya**.

Dr Krishna Ella, Chairman & Managing Director, Bharat Biotech, said, “Despite the lack of demand for COVID-19 vaccines, we continued product development in intra nasal vaccines to ensure that we are well prepared with platform technologies for future infectious diseases."

Likewise, AstraZeneca and the University of Oxford are also testing an intranasal version of the vaccine.

Aerosol vaccine: In June 2022, scientists at McMaster University, Canada announced a unique inhaled aerosol form of COVID vaccine, better protection and stronger immunity than nasal sprays. Researchers report that, as opposed to nasal sprays, inhaled aerosols bypass the nasal passage and deliver vaccine droplets deep inside the airway, where they can trigger a broad immune response.

"The immune response generated when vaccine is delivered deep into the lung is much stronger than depositing the vaccine material in the nose and throat because of the anatomy and nature of the tissue and the immune cells that are available to respond are very different," explains **Matthew Miller, a co-author of the study who holds the Canada Research Chair in Viral Pandemics at McMaster University**.

"This study for the first time provides strong preclinical evidence to support the development of inhaled aerosol delivery over nasal spray for human vaccination against respiratory infections including TB, COVID-19 and influenza," says**Zhou Xing, co-investigator of the study and a professor at the McMaster Immunology Research Centre and Department of Medicine**

Furthermore, CanSino Biologics’s inhaled vaccine, “Convidecia Air" is approved by China National Medical Products Administration (NMPA) as COVID-19 booster dose. Utilising the same adenovirus vector technological platform as the intramuscular version Convidecia, “Convidecia Air" provides a non-invasive option that uses a nebulizer to change liquid into an aerosol for inhalation through the mouth. Convidecia Air is needle-free and can effectively induce comprehensive immune protection in response to SARS-CoV-2 after just one breath. In addition, Convidecia Air can be stably transported and stored between 2°C and 8°C, compatible for mass vaccination.

CanSino and Bharat have cleared regulatory hurdles, and they will be available soon. As per WHO data, globally there are 172 vaccines in clinical development, including two inhaled formulations and 12 nasal-spray formulations, including two that have been approved.
Dissolvable microneedles Patch vaccines

Microneedles (MNs) are arrays of micrometer-sized solid fabricated needle projections that can painlessly deliver therapeutics into the epidermis/dermis. Microneedle patches designed to precisely deliver vaccines into the intradermal space, rich in immune cells, provide a noninvasive and self-applicable vaccination approach, eliminating the need for hypodermic needles and trained medical personnel for vaccine administration.

Dissolving microneedles (DMNs) are miniature needles made of polymers such as polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), and polyglycolic acid (PGA) that dissolve in the skin to deliver encapsulated medicines, leaving no sharp waste. Transdermal vaccination using biodegradable microneedles ensures controlled release of drugs via a dissolvable microneedle that improves dosing accuracy and ensures precise vaccine delivery.

Several companies are developing a microneedle patch to administer vaccines. The microneedles are impregnated with a vaccine that targets immune cells in the dermis. Patches are being investigated as a potential alternative to intramuscular vaccines for influenza and COVID-19.

In addition, 3D-printed microneedles improve vaccine retention in the skin, activate immune cells, and stimulate humoral and cellular immune responses in comparison to conventional mode.

The microneedle array is similar to band-aid patches and provides cold-chain storage avoidance and self-administration flexibility. However, microneedles only offer either rapid or sustained release, which limits their application in vaccine administration. A transdermal microneedle device with programmable pulsatile or delayed burst release with various desired lag times is needed to replicate traditional immunisation.

The UK based Emergex Covid-19 microneedle patch by Oxfordshire company has developed skin patch to administer a T-cell vaccine. Emergex, is owned by Singaporean venture capital firm Vickers Venture Partners.

In May 2022, Emergex Vaccines announced that its COVID-19 vaccine candidate, “synthetic CD8+ T cell Adaptive Vaccines" can be successfully coated onto Zosano Pharma’s Micro-Needle Patch system. Zosano’s patch consists of an array of approximately two thousand drug-coated titanium microneedles mounted on an adhesive patch that is administered to the skin using a reusable applicator. Emergex’s COVID-19 vaccine is stable on the patches over a wide temperature range for up to six months at 40°C/ 75 per cent relative humidity, reducing cold chain logistics.

“Our T cell Adaptive Vaccine technology has the potential to provide broad immune protection – covering viral strains and escape mutations as well as cellular immune memory that may last for decades. Innovative, easy-to-use patch delivery could radically transform the vaccine landscape” says **Robin Cohen, Chief Commercial Officer at Emergex**.

University of Queensland, Australia, developing a next-gen vaccine delivery system using a technology called the high-density microarray patch (HD-MAP), of 7x7 mm with 5,000 needle-like protrusions that are able to pierce the skin and deposit the vaccine into the immune-rich epidermal and dermal tissue layers without pain or skin bleeding. The patch can be stored stably at room temperature for up to 1 month.

Further, in November 2021, India’s Zydus Cadila (now renamed as Zydus Lifesciences) received the EUA for ZyCoV-D in India, the world’s first needle-free Plasmid DNA Vaccine for COVID-19. The vaccine, ZyCoV-D, is exclusively administered using the PharmaJet Tropis Needle-free Injection System. And in April 2021, a new continuous needleless injection system called Comfort-M was launched in Korea by MIKA MEDICAL.

The new study, by The Catholic University of America, and The University of Texas Medical Branch, in July 2022 reported the first non-infectious, bacteriophage T4-based, multicomponent, needle and adjuvant-free mucosal vaccine. The needle-free “mucosal bacteriophage (phage) T4-based COVID-19 vaccine” is effective against SARS-CoV-2 infection.

According to a study report published in July this year in ScienceDaily, This intranasally administered vaccine generates superior mucosal immunity in mice in addition to inducing robust humoral and cell-mediated immune responses, and provides complete protection and sterilising immunity against SARS-CoV-2 variants. The vaccine is stable, adjuvant-free and cost-effectively manufactured and distributed, making it a strategically important next-generation COVID-19 vaccine for ending this pandemic. This modular, needle-free, phage T4 mucosal vaccine delivery platform is an excellent candidate to design efficacious mucosal vaccines against other respiratory infections and for emergency preparedness against emerging epidemic and pandemic pathogens.

Bivalent and Trivalent recombinant vaccines

Vaccines companies are adopting a recombinant bivalent and trivalent vaccines approach against SARS-CoV-2 and influenza viruses due to limitations at monovalent vaccines. Majority emerging vaccine researchers anticipate bivalent/trivalent vaccine platforms to create vaccines against resurgent SARS-CoV-2 variants and IAV infections.

In early September 2022, China's Sinovac trivalent COVID-19 vaccine progressed as the world's first study researching multivalent inactivated COVID-19 vaccine. The clinical trial will evaluate the immunogenicity and safety of one booster dose of the two candidate vaccines in adults who had received two booster doses of CoronaVac, mRNA, or adenovirus vector COVID-19 vaccine.

Similarly, Australian biopharma EnGeneIC is developing the world’s first COVID-19 vaccine able to offer immunity against all variants. The 2nd Gen vaccine produces “high affinity” antibodies that neutralise all COVID-19 variants.

EnGeneIC is currently conducting anti-COVID-19 vaccine trials with its patented platform technology based around a biological nanocell (EDV; EnGeneIC Dream Vector) in Sydney and Melbourne. Initially developed as a breakthrough in cancer treatment, these EDVs are loaded with anti-viral molecules to deliver a world-first “Nano-cellular COVID-19 vaccine”. The COVID-19 EDV vaccine from EnGeneIC is also believed to be effective in immunocompromised people.

It may be noted that in mid May 2022, India’s Bharat Biotech International Ltd (BBIL), has collaborated with University of Sydney, Australia and ExcellGene SA, Switzerland for developing a ‘variant-proof’ COVID-19 vaccine fighting both current and future variants of viruses.

World’s first plant-based vaccine

In February 2022, Medicago, a Canada-headquartered biopharma company, and GlaxoSmithKline (GSK) announced that Health Canada has granted approval for COVIFENZ, COVID-19 vaccine, (plant-based virus-like particles [VLP], recombinant, adjuvanted). With “positive efficacy and safety results" world's first plant-based vaccine. This vaccine is indicated for active immunisation to prevent coronavirus disease 2019 (COVIDÃ¢â?¬â??19) caused by severe acute respiratory syndrome coronavirus 2 (SARSÃ¢â?¬â??CoVÃ¢â?¬â??2) in individuals 18 to 64 years of age.

Health Canada based its decision on scientific data shared by Medicago as part of their rolling submission that began in April 2021 under an Interim Order, and concluded with the filing of a New Drug Submission-CV.

COVIFENZ uses Coronavirus-Like Particle (CoVLP) technology with the vaccine composed of recombinant spike (S) glycoprotein expressed as virus-like particles (VLPs) co-administered with GSK’s pandemic adjuvant. The vaccination regimen calls for two doses given intramuscularly 21 days apart (3.75 micrograms of CoVLP antigen in combination with GSK pandemic adjuvant in the same injection). The vaccine is stored at 2 °C to 8 °C. COVIFENZ antigen will be manufactured in Canada and in North Carolina (US).

From a plant similar to tobacco plant, a mimicking particle is extracted and is combined with an adjuvant made by GSK, for immune reaction following administration. The Japanese firm, Mitsubishi Tanabe Pharma Corporation (MTPC) Group, is the parent company of Medicago.

What does the future hold?

SARS-CoV-2 continues to emerge over time, while new virus variants arise and threaten to reduce the impact of existing vaccine efforts. Clearly, strategies are needed to deal with emerging variants and to safeguard populations against potential health threats in the future. Structure-based vaccine development, new vaccine platforms, and automation are key to overcoming current vaccine development challenges. Technology advances have enabled the development of vaccines with increased efficiency within shorter time frames, as demonstrated by COVID-19. These novel approaches and development strategies are expected to pave the way to developing vaccines against diseases where traditional approaches have failed.

Hithaishi C Bhaskar

hithaishi.cb@mmactiv.com