Emerging Vaccine Pipeline

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Disclosures

• *I do not have any disclosures or conflicts of interests.*

• *For today’s presentation, companies that produce vaccines may be mentioned due to the nature of discussing vaccine products in the pipeline. Company and/or brand names will be used sparingly and when appropriate, for educational purposes only, and will be presented objectively as source references, without bias toward or against any particular product or company.*

Presentation Note

○ Material presented is as up-to-date as possible in preparation for today’s presentation.

○ Information changes rapidly and new data need to be assessed and incorporated regularly.

○ Medical science and clinical practice must adapt in agile ways to recommend and implement the best information and safest practices known at any given time.
Learning Objectives

1) Identify infectious disease targets for vaccines in the pipeline
2) Recognize various mechanisms of immune modulation that guide vaccine development
3) Describe research efforts in novel vaccine delivery methods

Pediatric providers have strong knowledge of current childhood vaccines since such products are a critical part of medical care for children. However, knowledge regarding vaccine innovation and products in development may be more limited.

Understanding advancements in immune-based therapeutics, disease prevention, and vaccine delivery methods helps providers to appropriately counsel patients and families on current and new vaccine product options to provide the best care.
General Vaccination Concepts

“The main principle of vaccination is the proactive induction of a protective immune response by mimicking the natural interaction of an infectious pathogen (bacteria, viruses, etc.) with the human immune system.”


Several different vaccine end points or goals can be targeted to determine if vaccine is effective

- These are different for every infectious agent and every vaccine
- The approach(es) for determining these goals follow consistent processes within many agencies to ensure standards and safety

3 general use goals
1) Protect an individual
2) Protect a population
3) Control an outbreak

4 outcome-based goals
1) Prevent mortality
2) Prevent severe illness/complications
3) Prevent disease
4) Prevent transmission
General Vaccination Concepts

“The main **principle of vaccination** is the proactive induction of a protective immune response by mimicking the natural interaction of an infectious pathogen (bacteria, viruses, etc.) with the human immune system.”


- Several different vaccine end points or goals can be targeted to determine if vaccine is effective
  - These are different for every infectious agent and every vaccine
  - The approach(es) for determining these goals follow consistent processes within many agencies to ensure standards and safety

- Prevent people from dying
  - ↓ Overall mortality
  - ↓ Age-dependent mortality
  - ↓ Population mortality

- Prevent disease (people getting sick)
  - ↓ Severe disease (symptoms)
  - ↓ Moderate disease (symptoms)
  - ↓ Any disease (symptoms)

- Prevent complications and long-term issues from infection
  - ↓ ICU care/high level support
  - ↓ Hospitalizations
  - ↓ Complications from disease

- Prevent pathogen transmission
  - ↓ Horizontal transmission
    *(community spread, person-to-person)*
  - ↓ Vertical transmission
    *(mother to baby during pregnancy or delivery)*
Developing new vaccine products

We need knowledge of...

1) Human immune response to a pathogen (expected & aberrant)
2) Animal model that predicts human protection/response
3) Clear immunologic correlates of protection (lab-based, measurable)
4) Large trials with long-term follow-up (at least 3 years preferred)
5) Funding priorities (public and/or private)
Developing Covid-19 Vaccines at Pandemic Speed

Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M.

Traditional Paradigm — Multiple Years

- Small-scale clinical trial material
- Manufacturing scale-up, commercial scale, validation of process
- Large-scale manufacturing

- Target ID, development partner selection, and preclinical trial
- Phase 1
- Phase 2a
- Phase 3
- Licensure

- Go or no-go decision to invest in candidate
- First trial in humans
- Efficacy trial in humans
- Evaluation trial in humans

Outbreak Paradigm — Overlapping Phases Shorten Development Time

- Target ID, development partner selection, and preclinical trial
- Clinical development
- Safety/dose selection
- Safety/efficacy
- First in humans (safety)
- Efficacy trial
- Regulatory pathway for emergency authorization

- Manufacturing development, scale-up, clinical trial material, commercial scale, validation of process
- Large-scale manufacturing

Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.

The pandemic paradigm requires multiple activities to be conducted at financial risk by developers and manufacturers and without knowing whether the vaccine candidate will be safe and effective, including very early manufacturing scale-up to commercial scale before establishment of clinical proof of concept. ID denotes identification.

Unprecedented speed

Typical development

8-15 years

Accelerated course

High risk groups

Benefit >> Risk?

Broad application

minimum 12-18 mos

Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

Vaccine Strategy, Planning and Funding – U.S.

VACCINES

National Strategic Plan
for the United States | 2021–2025

Federal Implementation Plan
for the United States | 2021–2025

VISION

The United States will be a place where vaccine-preventable diseases are eliminated through safe and effective vaccination over the lifespan.

Goal 1: Foster innovation in vaccine development and related technologies.
Goal 2: Maintain the highest possible levels of vaccine safety.
Goal 3: Increase knowledge of and confidence in routinely recommended vaccines.
Goal 4: Increase access to and use of all routinely recommended vaccines.
Goal 5: Protect the health of the nation by supporting global immunization efforts.

www.hhs.gov/vaccines/vaccines-national-strategic-plan/index.html
Improved understanding of the pathogen-host interaction and the human immune system have led to innovations in the following areas:

- **Vaccine design** (e.g., advances in nucleic acid vaccine development)
- **Novel antigen delivery platforms**
  (e.g., liposomes, nanoparticles, and novel protein expression systems such as plant-based systems)
- **Promising vaccine delivery mechanisms** (e.g., microneedle patch)

Other advances include
- Structure-based vaccine design
- Machine-learning to identify and design antigens
- Novel adjuvants
- Alternative routes of vaccine administration (e.g., transdermal)
NVAC Innovation in Immunization Subcommittee

Charge from the Assistant Secretary for Health

Develop report with recommendations outlining vaccine innovation agenda
• Describes vaccine innovation priorities
• Describe actions for advancing the development of new and existing vaccines
• Optimize public health and reduce disease burden in the United States

The final report should be ready for vote by the February 2024 NVAC meeting.

The charge states that NVAC should write a report that includes:

- Review of both conventional and promising novel approaches for vaccine discovery and development as well as recommendations for actionable, high-impact activities that HHS and federal partners can take to advance clinical trial design, regulatory requirements, manufacturing processes, funding mechanisms, and business models; including ways we can leverage emerging technologies, processes, and workflows and suggestions for innovative collaborations.

- Evidence-based approach for identifying and prioritizing vaccine candidates and immunization technologies including their criteria for prioritization. NVAC should take the potential impact on disease burden, population health outcomes, health equity, economic impact, national health priorities, and scientific feasibility into account in the development of the approach.

- List of vaccination innovation priorities, including target antigens, molecular platforms, and immunization delivery technologies.

- Forward-looking approach to introduce vaccines for special patient populations and neglected diseases to portray their value and importance.

- Scientific agenda outlining a framework of research direction and identifies scientific needs and gaps that should be addressed by end of 2028.

NVAC should create a working group
• Select NVAC members, Federal and non-federal stakeholders, Ex-officio and liaison members of NVAC and additional experts not on NVAC

www.hhs.gov/vaccines/nvac/index.html
Vaccine Strategy, Planning and Funding – Global

Resources, Funding, Collaboration, Innovation

www.gavi.org/


www.who.int/health-topics/vaccines-and-immunization#tab=tab_1

www.path.org/
www.path.org/resources/path-2022-annual-report/

www.unicef.org/innovation/vaccine-microarray-patches-vmaps

https://medicalcountermeasures.gov/barda/

https://wellcome.org/

https://cepi.net/

Sampling of organizations working toward reducing the burden of infectious diseases worldwide
...and many more!
Fig. 2 | Distribution of vaccine candidates by geographic location and type of developer

www.nature.com/articles/d41573-023-00119-4

68% of candidates are being developed independently or collaboratively by private companies/industry
25% are being developed by academic or other non-profit organizations

a) Vaccine candidates with developers from the USA, China and western Europe, categorized by technical platform
Fig. 2 | Distribution of vaccine candidates by geographic location and type of developer

www.nature.com/articles/d41573-023-00119-4

- 68% of candidates being developed independently or collaboratively by private companies/industry
- 25% being developed by academic or other non-profit organizations

a) Vaccine candidates with developers from the USA, China and western Europe, categorized by technical platform

b) Candidates for the top six diseases for vaccine development, by type of developer.
Infectious disease targets for vaccines in the pipeline
## Pathogen targets for vaccine product development

<table>
<thead>
<tr>
<th>NEW</th>
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</tr>
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<tbody>
<tr>
<td><em>Borrelia burgdorferi</em> (Lyme disease)</td>
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<td>RSV (active and passive immunity)</td>
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<td>EBV</td>
<td>Measles</td>
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<td>HSV</td>
<td>HPV</td>
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<td>Gonorrhea</td>
<td>Tuberculosis</td>
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<td>Zika virus</td>
<td>Malaria</td>
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<tr>
<td>Norovirus</td>
<td>Ebola</td>
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<tr>
<td><em>C. difficile</em></td>
<td><em>Salmonella typhi</em></td>
</tr>
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...and many more in early studies...
# Pathogen targets for vaccine product development

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...and many more in early studies...
Lyme Disease  ➡️  Borrelia burgdorferi

**Modernapipeline:** two novel mRNA vaccine candidates against Borrelia species (Lyme disease)

- **mRNA-1982**
  - monovalent vaccine targeting prevalent US serotype

- **mRNA-1975**
  - multivalent, includes 7 RNAs targeting 7 European serotypes
  - Europe - Phase 1/2 study, 800 subjects
  - Anticipate results informing immunogenicity in 2024

**Penn Medicine**

Development of an mRNA-lipid nanoparticle vaccine against Lyme disease

- **VLA15-221 Phase 2 study** showed a strong anamnestic antibody response for all serotypes in pediatric (5 to 11 years of age) and adolescent participants (12 to 17 years of age), as well as in adults (18 to 65 years of age), one month after administration of a booster dose (month 19).

**Pfizer and Valneva partnership**

- July 2017: Fast Track designation by US FDA (Valneva)
- April 2020: Collaboration agreement between Valneva and Pfizer to co-develop VLA15 (updated June 2022)

"Safety and tolerability profile of VLA15 after a booster dose was consistent with previous studies as the vaccine candidate was well-tolerated in all age groups regardless of the primary vaccination schedule."

"No vaccine-related serious adverse events (SAEs) and no safety concerns were observed by an independent Data Safety Monitoring Board (DSMB)."

**Lyme Disease → Borrelia burgdorferi**

**VLA15 (Pfizer/Valneva) – Phase III trials**

Investigational multivalent protein subunit vaccine - Targets outer surface protein A (OspA) of *B. burgdorferi*

- OspA: surface protein expressed by *B. burgdorferi* when present in a tick; blocking OspA limits transmission
- Vaccine covers 6 most common OspA serotypes (*B. burgdorferi sensu lato* species prevalent N. America, Europe)
- Alum-adjuvanted formulation; administered intramuscularly

**An Efficacy, Safety, Tolerability, Immunogenicity, and Lot-Consistency Clinical Trial of a 6-Valent OspA-Based Lyme Disease Vaccine (VLA15) (VALOR)**

ClinicalTrials.gov ID: NCT05477524
Sponsor: Pfizer  Last Update Posted: 2023-11-28

[https://clinicaltrials.gov/study/NCT05477524](https://clinicaltrials.gov/study/NCT05477524)

**Phase 3 trial**

3-dose primary vaccination series at about 0, 2, and 5 to 9 months and then receive a booster dose about 12 months later.

...primary series completed before peak Lyme disease season followed by a booster dose just prior to beginning of second Lyme disease season.

**Safety Study of a Vaccine to Help Protect Against Lyme Disease in Healthy Children**

ClinicalTrials.gov ID: NCT05634811
Sponsor: Pfizer  Last Update Posted: 2023-10-25

*Initiated Dec 2022, estimated completion mid-2025*

**Phase 3** trial

3-dose primary vaccination series at about 0, 2, and 5 to 9 months and then receive a booster dose about 12 months later.

...primary series completed before peak Lyme disease season followed by a booster dose just prior to beginning of second Lyme disease season.

**Anticipate 2026...**
Pre-exposure antibody prophylaxis (passive immunity - LymePrep) to prevent Lyme Disease in endemic regions

MassBiologics at UMass Chan Medical School
www.jci.org/articles/view/144843/pdf

A Phase 1 Study in Healthy Subjects to Evaluate the Safety and Pharmacokinetics of a Human Monoclonal Antibody (2217LS) Against Borrelia Burgdorferi (B. Burgdorferi) Outer Surface Protein A (OspA)
ClinicalTrials.gov ID: NCT04863287
Sponsor: MassBiologics  Last Update Posted: 2022-09-16
https://clinicaltrials.gov/study/NCT04863287

Purpose of study
1) Learn about safety and tolerability of subcutaneous (SC) injection of 2217LS when administered to healthy volunteers
2) Find out how much 2217LS is in the blood of healthy volunteers after receiving 2217LS SC

Competition to accelerate development of Lyme disease diagnostics
U.S. Department of Health and Human Services (HHS) and the Steven & Alexandra Cohen Foundation

LymeX Diagnostics Prize timeline

Phase 1 was open to all eligible entrants to submit concept papers and plans for development. In Phase 2, 10 teams are participating in a virtual accelerator to help them refine their concepts.

Ultimate Goal
To nurture development of next-generation diagnostics toward Food and Drug Administration review.

Potential for awarding up to $10 million in prizes across all potential phases subject to availability of funds

www.lymexdiagnosticsprize.com/
CONCLUSIONS

...there are numerous candidate CMV vaccines in development, both those targeted to prevent congenital infection and those targeted to prevent posttransplant infections.

...early evidence from Phase II trials that vaccination can prevent acquisition of CMV by seronegative women exposed to CMV in nature, and there is solid evidence that CMV disease in seronegative solid organ recipients and in hematogenous stem cell recipients can be prevented.

There are as yet no Phase III data, but numerous candidate vaccines are moving forward, including several aimed at the goal of preventing congenital CMV disease.
Cytomegalovirus (CMV) ➔ Specific populations

A Phase 3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1647 Cytomegalovirus (CMV) Vaccine in Healthy Participants 16 to 40 Years of Age

ClinicalTrials.gov ID: NCT05085366
Sponsor: ModernaTX, Inc.
Last Update Posted: 2023-11-21
https://clinicaltrials.gov/study/NCT05085366

**CMVictory Trial**

The main purpose of this study is to evaluate:

- Efficacy of mRNA 1647 vaccine in CMV-seronegative female participants
- Safety and reactogenicity of mRNA-1647 vaccine in all participants

*Initiated October 2021, estimated completion mid-2026*

“**It is exciting that for the first time in the 50 years of CMV vaccine development we have a phase 3 trial underway**”

Sallie Permar, MD, PhD
NewYork-Presbyterian/Weill Cornell Medical

in recent interview with Managed Healthcare Executive

www.managedhealthcareexecutive.com/view/cytomegalovirus-update-for-the-first-time-a-phase-3-vaccine-trial-idweek-2023
Innovative global partnership between public, private, philanthropic, and civil society organisations

ACTIVE CEPI-FUNDED VACCINE CANDIDATE PORTFOLIO BY PHASE

<table>
<thead>
<tr>
<th>Lassa</th>
<th>MERS-CoV</th>
<th>Nipah</th>
<th>Rift Valley</th>
<th>Chikungunya</th>
<th>SARS-CoV-2</th>
<th>Broadly protective coronavirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predclinical</td>
<td>University of Oxford/Janssen</td>
<td>Themis</td>
<td>University of Oxford/Janssen</td>
<td>Colorado State U</td>
<td>Sidra Medicine</td>
<td>SK Bioscience</td>
</tr>
<tr>
<td>Phase I</td>
<td>Emergent</td>
<td>University of Oxford/Janssen</td>
<td>DiZo Vaccines</td>
<td>VIDO</td>
<td>CPI/CalTech</td>
<td>Biological E</td>
</tr>
<tr>
<td>Phase II</td>
<td>IAVI</td>
<td>IDT</td>
<td>PHIV</td>
<td>Virostat</td>
<td>VBI</td>
<td>Moderna</td>
</tr>
<tr>
<td>Phase IIb/III &amp; III</td>
<td>Themis</td>
<td></td>
<td></td>
<td>Wageningen U.</td>
<td></td>
<td>Clover</td>
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<tr>
<td>Registration</td>
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<td></td>
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<td>Novavax</td>
</tr>
</tbody>
</table>

(l) CEPI has also funded booster studies of SARS-CoV-2 vaccines developed by Medigen and Vaxxinity
Chikungunya Virus (CHIKV)

VLA1553 is a live-attenuated vaccine for active immunization and prevention of disease caused by chikungunya virus

March 2022: Phase 3 data reported in 4,115 adults aged 18 years and above showing a 98.9% seroresponse rate at 28 days with single vaccination

June 2023: Results published in Lancet
The Lancet subsequently published these results in June 2023.
Final lot-to-lot consistency results were published in May 2022, twelve-month persistence data in December 2022, and adolescent data in November 2023.
Follow-up study underway to monitor 5-year immune response data (NCT04838444).

November 2023
VLA1553 received U.S. FDA approval under brand name IXCHIQ® (Valneva)
Indicated for prevention of disease caused by CHIKV in individuals 18 years of age and older who are at increased risk of exposure to CHIKV.

Continued approval in US is contingent upon verification of clinical benefit in confirmatory studies.
VLA1553 is also under accelerated assessment by the European Medicines Agency (EMA) and a standard regulatory review is underway with Health Canada.
Tuberculosis

no new approved vaccine in 102 years since BCG

BCG: the first vaccine for tuberculosis

Tuberculosis has been an infectious scourge throughout human history. Working in France, Albert Calmette and Camille Guérin developed their eponymous live attenuated vaccine for tuberculosis (BCG) and used it for the first time to protect at-risk infants. Read More

By Zoltan Fehervari

www.nature.com/immersive/d42859-020-00005-8/index.html

Nature Milestones in Vaccines
The council will work to boost the tuberculosis vaccine pipeline and facilitate the licensing and use of safe and effective tuberculosis vaccines, through partnership-based, innovative solutions to close crucial gaps in knowledge and financing.
Tuberculosis Vaccine Goals – one organization

**Vaccines**

- Develop a **new TB vaccine by 2025**.
- Diversify and **broaden the pipeline of next-generation TB vaccine candidates** by expanding research on Mtb immunology and basic mycobacteriology and develop animal models that better reflect human infection and disease.
- Provide resources and support to **efficiently** move a diverse range of vaccine concepts from the laboratory to the clinic.
- Significantly **accelerate clinical development of vaccine candidates** and ensure sufficient financing, resources and capacity to advance multiple promising candidates through efficacy trials and licensure without delay.
- Conduct research on correlates of **vaccine-induced protection** during vaccine efficacy trials to inform vaccine design, expedite clinical trials of future vaccine candidates.
- Work with countries and affected communities to prepare for **successful licensure and roll-out** of new TB vaccines once licensed.

**Research Goals**

Accelerate development of new tools to prevent, diagnose and treat TB by identifying innovative product-development pathways and improving collaboration among actors in product development.
Tuberculosis

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 16 vaccine candidates in the pipeline as of September 2023, of which 11 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

Information reported by vaccine sponsors or found in clinical trial registries or other public sources.
For the full list of completed trials for each candidate, visit [www.newtbvaccines.org/tb-vaccine-pipeline/](http://www.newtbvaccines.org/tb-vaccine-pipeline/)

Last update: 28 September 2023
Tuberculosis

From the website:
TBVI is continuously working on supporting the development of new vaccine candidates. Vaccine developers are kindly invited to share an update if needed by contacting TBVI.

www.tbvi.eu/what-we-do/pipeline-of-vaccines/

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www.tbvacpathway.org/
Nearly 100 years later...

Several promising candidates:

- O-antigen conjugate vaccines are most advanced candidates
- Live attenuated and subunit vaccines are also in clinical trials

Figure 2. Shigella Vaccine Development History—major achievements and influences (LPS-lipopolysaccharide, TT-tetanus toxoid).
A Phase 1/2a Double-Blind, Randomized, Placebo-Controlled Trial to Assess the Safety and Efficacy of Oral Administration of the Bacteriophage Preparation, ShigActive™, in a Human Experimental Model of Shigellosis With Shigella Flexneri 2a Strain

ClinicalTrials.gov ID: NCT05182749
Sponsor: Intralytix, Inc.   Last Update Posted: 2023-10-10
https://clinicaltrials.gov/study/NCT05182749

Detailed Description
Purpose: determine if ShigActive is safe and effective in healthy adults in a continuous Phase 1/2a trial

  • **Phase 1:** assess the safety of ShigActive in healthy adults
  • **Phase 2a:** evaluate the safety and efficacy of ShigActive in healthy adults after a challenge with Shigella

Initiated Feb 2023, estimated completion mid-2025

Verbiage copied from study description:

**ShigActive is a collection of bacteriophages.**

Bacteriophages (or phages) are viruses that infect only bacteria.

The phages in ShigActive infect a specific type of bacteria called Shigella, which is the causative agent of shigellosis or dysentery.

**ShigActive is intended to significantly reduce or eliminate Shigella levels in the human gastrointestinal tract,** which in turn, is anticipated to reduce the incidence and/or severity of shigellosis.
Influenza Vaccines Research and Development (R&D) Roadmap (IVR)
Created to promote influenza vaccine R&D, through extensive international stakeholder engagement process

The roadmap covers a 10-year timeframe and is organized into six sections:

1) Virology
2) Immunology
3) Vaccinology for seasonal influenza vaccines
4) Vaccinology for universal influenza vaccines
5) Animal and human influenza virus infection models
6) Policy, finance, and regulation

- 113 specific R&D Milestones
- 37 designated “high priority”
Influenza → Defining “universal influenza vaccine”

<table>
<thead>
<tr>
<th>Source</th>
<th>Definitions</th>
<th>Target viruses</th>
<th>Duration of protection</th>
<th>Target population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation Grand Challenges Initiative [15]</td>
<td><strong>Universal influenza vaccines</strong>: “protection from morbidity and mortality caused by all subtypes of circulating and emerging (drifted and shifted) influenza A subtype viruses and influenza B lineage viruses for at least 3–5 years.”</td>
<td>All influenza A viruses and influenza B viruses</td>
<td>Minimum of 3–5 years</td>
<td>All age groups, especially in developing countries</td>
</tr>
<tr>
<td>European Commission European Union–India Collaboration for Next Generation Influenza Vaccines [14]</td>
<td><strong>Next-generation influenza vaccines</strong>: improved efficacy and safety; improved duration of immunity; reactivity against an increased breadth of influenza strains and/or from the outset of a large-scale influenza pandemic; suitable for different populations and LMICs.</td>
<td>Increased breadth of influenza strains</td>
<td>Improved duration of immunity</td>
<td>Different populations and LMICs</td>
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<td>Global Funders Consortium for Universal Influenza Vaccine Development [26]</td>
<td><strong>Universal influenza vaccine</strong>: high efficacy; induces immunity to a broad array of influenza A viruses (and perhaps influenza B viruses); prevents severe disease; confers more durable immunity than current vaccines; prevents seasonal and pandemic influenza; cost-effective for low- and high-resource settings.</td>
<td>Influenza A viruses and perhaps influenza B viruses</td>
<td>More durable than current influenza vaccines</td>
<td>All</td>
</tr>
<tr>
<td>National Institute of Allergy &amp; Infectious Diseases A Universal Influenza Vaccine: The Strategic Plan for the NIAID [16]</td>
<td><strong>Universal influenza vaccine</strong>: goal of at least 75% effectiveness against symptomatic influenza virus infection; protects against Groups 1 and Group 2 influenza A viruses (secondary target, influenza B viruses); durable protection for at least 1 year and preferably through multiple seasons; suitable for all age groups.</td>
<td>Group 1 and Group 2 influenza A viruses</td>
<td>Durable protection for at least 1 year</td>
<td>All age groups</td>
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<tr>
<td>Sabin-Aspen Vaccine Science &amp; Policy Group Accelerating the Development of Universal Influenza Vaccine [25]</td>
<td><strong>Universal influenza vaccine</strong>: safe and highly effective in all age groups, against any strain; confers lifelong immunity.</td>
<td>All influenza viruses</td>
<td>Lifelong</td>
<td>All age groups</td>
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<tr>
<td>World Health Organization Preferred Product Characteristics for Next-Generation Influenza Vaccines [8]</td>
<td><strong>Universal-type influenza A vaccine</strong>: protection against severe influenza A virus illness for at least 5 years; suitable for high-risk groups in LMICs.</td>
<td>Influenza A viruses</td>
<td>At least 5 years</td>
<td>High-risk groups in LMICs</td>
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</table>

**Abbreviations:** LMICs, low- and middle-income countries; NIAID, US National Institute of Allergy and Infectious Diseases.
Influenza ➔ Search for the elusive universal vaccine

3 Nucleic acid-based
Moderna (2)
Pfizer/BioNTech (1)

1 Non-VLP nanoparticles
Novovax/Emergent BioSolutions (1)

1 Recombinant protein
BiondVax Pharmaceuticals (1)

1 Virus-like particles (VLP)
Medicago (1)

Phase 3 trials

https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape
Pathogen targets for vaccine product development

NEW

✓ *Borrelia burgdorferi* (Lyme disease)
✓ CMV (specific populations)
HIV
EBV
HSV
Gonorrhea
Zika virus
Norovirus
*C. difficile*

IMPROVE on existing

✓ Influenza - Universal
RSV (active and passive immunity)
SARS-CoV-2
Measles
HPV
✓ Tuberculosis
Malaria
Ebola
*Salmonella typhi*

...and many more in early studies...
Mechanisms of immune modulation that guide vaccine development
Types of Vaccines

Currently available vaccine types

- Live attenuated
- Killed/Inactivated (whole organism)
- Toxoid
- Subunit (purified protein, recombinant protein, polysaccharide, peptide)
- Virus-like particle (VLP)
- Outer membrane vesicle
- Protein-polysaccharide conjugate
- Viral vectored (Ebola)
- Nucleic acid vaccine (SARS-CoV-2)

Fig. 2 | Different types of vaccine. Schematic representation of different types of vaccine against pathogens; the text indicates against which pathogens certain vaccines are licensed and when each type of vaccine was first introduced.

BCG, Mycobacterium bovis bacillus Calmette–Guérin.
Fig. 1 | Landscape of vaccine candidates by technology platform, R&D phase and disease

www.nature.com/articles/d41573-023-00119-4

a) The 966 vaccine candidates were classified into the categories shown based on the underlying technology platforms.

Products with inadequate information for classification were included in an ‘Unknown’ group, and those not fitting into the main groups were included in an ‘Others’ group.
Fig. 1 | Landscape of vaccine candidates by technology platform, R&D phase and disease

a) The 966 vaccine candidates were classified into the categories shown based on the underlying technology platforms.

Products with inadequate information for classification were included in an ‘Unknown’ group, and those not fitting into the main groups were included in an ‘Others’ group.

b) All candidates excluding ‘Unknown’ and ‘Others’ are shown in the bar chart, classified by R&D phase.
c) Proportion of vaccine candidates against different diseases. Diseases with less than ten candidates were included in the ‘Others’ group.
Fig. 1 | Landscape of vaccine candidates by technology platform, R&D phase and disease

www.nature.com/articles/d41573-023-00119-4

c) Proportion of vaccine candidates against different diseases. Diseases with less than ten candidates were included in the ‘Others’ group.

d) Candidates for the top six diseases for vaccine development, by technology platform.
mRNA vaccines have emerged as highly effective strategies in the prophylaxis and treatment of diseases, thanks largely although not totally to their extraordinary performance in recent years against the worldwide plague COVID-19. The huge superiority of mRNA vaccines regarding their efficacy, safety, and large-scale manufacture encourages pharmaceutical industries and biotechnology companies to expand their application to a diverse array of diseases, despite the nonnegligible problems in design, fabrication, and mode of administration. This review delves into the technical underpinnings of mRNA vaccines, covering mRNA design, synthesis, delivery, and adjuvant technologies. Moreover, this review presents a systematic retrospective analysis in a logical and well-organized manner, shedding light on representative mRNA vaccines employed in various diseases. The scope extends across infectious diseases, cancers, immunological diseases, tissue damages, and rare diseases, showcasing the versatility and potential of mRNA vaccines in diverse therapeutic areas. Furthermore, this review engages in a prospective discussion regarding the current challenge and potential direction for the advancement and utilization of mRNA vaccines. Overall, this comprehensive review serves as a valuable resource for researchers, clinicians, and industry professionals, providing a comprehensive understanding of the technical aspects, historical context, and future prospects of mRNA vaccines in the fight against various diseases.
# Future potential of mRNA vaccines

## Major mRNA vaccine trial results expected in 2023

<table>
<thead>
<tr>
<th>mRNA vaccine</th>
<th>Indication</th>
<th>Event</th>
<th>Trial size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna’s mRNA-1010</td>
<td>Seasonal influenza</td>
<td>Phase III results expected Q1</td>
<td>6,102 subjects</td>
</tr>
<tr>
<td>Pfizer’s modRNA vaccine</td>
<td>Seasonal influenza</td>
<td>Phase III results expected 2023</td>
<td>36,200 subjects</td>
</tr>
<tr>
<td>Roche's/BioNTech's RO7198457</td>
<td>Advanced melanoma</td>
<td>Phase II results expected H1</td>
<td>131 subjects</td>
</tr>
<tr>
<td>BioNTech's BNT-163</td>
<td>Herpes lesions</td>
<td>Phase I results expected H2</td>
<td>108 subjects</td>
</tr>
</tbody>
</table>

Source: GlobalData

Future potential of mRNA vaccines

Fig. 3 Landscape of mRNA vaccines in infectious diseases
mRNA vaccines have been developed against multiple infectious diseases to date, including severe acute respiratory syndrome coronavirus 2, zika virus, human immunodeficiency virus, influenza virus, cytomegalovirus, respiratory syncytial virus, varicella-zoster virus, and rabies virus.

Fig. 4 Landscape of mRNA vaccines in cancers
mRNA vaccines have been developed against multiple cancers to date, including melanoma, brain cancer, non-small cell lung cancer, ovarian cancer, prostate cancer, blood system cancer, digestive system cancer, and breast cancer.

Zhang, G; Tang, T; Chen, Y. et al. mRNA vaccines in disease prevention and treatment. *Sig Transduct Target Ther.* 2023; 8: 365.  
[www.nature.com/articles/s41392-023-01579-1](www.nature.com/articles/s41392-023-01579-1)
Research efforts in novel vaccine delivery methods
The sixth revolution in pediatric vaccinology: immunoengineering and delivery systems

Dheeraj Soni, Sharan Bobbala, Sophia Li, Evan A. Scott and David J. Dowling

Pediatric Research (2021) 89:1364–1372  www.nature.com/articles/s41390-020-01112-y

The 5 revolutions in vaccinology

1800s onwards; live attenuated smallpox, rabies, tuberculosis (BCG), yellow fever, polio (oral polio vaccine (OPV)) vaccines.

1950s: of the cornucopia of live vaccines made possible by passage in cell culture, the work by Enders, Robbins and Weller lead to the Salk and Sabin polio vaccines.

2000s; driving the immune system in the T helper 1 direction with stimuli such as vectors and adjuvants.

Combination vaccines: simultaneous administration of vaccines to target multiple diseases. The adjuvant toolbox: ranging from small-molecule adjuvants to combination adjuvants. Vaccines for non-infectious diseases: new treatments for tumors, allergy, or non-infectious disorders (e.g., prevention of drug overdose). Systems vaccinology: Systems biology approaches to identify predictors of vaccine efficacy and explore new insights about protective immunity. Reverse vaccinology: Bioinformatics aided vaccine design from pathogenic genetics. Immunomodulation and delivery systems: Delivering precise materials for specific activation of immune system (right time, right place, right size, right shape, etc.).
Vaccine Delivery Methods

Figure 1. Vaccine delivery routes.
“...highlights the significant potential of MAPs for vaccine delivery and underscores their versatility, safety, and potential for large-scale implementation.

The development and refinement of MAP-based vaccination approaches have the potential to transform the field of immunization, overcoming several barriers associated with traditional N&S injections.”
Novel delivery method: Microneedle/Microarray Systems


www.mdpi.com/2072-666X/12/4/435


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**Figure 2. Timeline of Microneedle Research Development.**

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**Figure 2. Different parenteral routes of vaccine administration.**

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**Fig. 4. Microarray patches (MAPs) enable precise, consistent, and minimally invasive administration of vaccine formulations (antigen + adjuvant) to immunologically rich cutaneous microenvironments, whereas conventional intramuscular (IM) immunization bypasses the skin immune system, results in systemic exposure to vaccine ingredients, and causes pain.**

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**References:**
Microarray Patches (MAPs): 5 types

**SOLID**

- Solid microneedles are applied to the skin
- Holes in the skin are created upon removal of the solid microneedles
- Topically applied cream diffuses through the holes into the skin created by the solid microneedles

**COATED**

- Tip of microneedle coated with vaccine
- Coated microneedles are applied to the skin depositing the vaccine
- Upon removal of the microneedles, the vaccine remains in the skin

**HOLLOW**

- Hollow microneedles loaded with vaccine/drug
- Hollow microneedles are applied into the skin
- Liquid formulation flows through the tip of the microneedle and into the skin

**DISSOLVABLE**

- Drugs/vaccines incorporated into microneedle by solvent coating with polymer melt
- Microneedles are applied to the skin
- Microneedles dissolve in the skin over time, leaving only the base of the microneedle array

**HYDROGEL**

- Hydrogel-forming patch with reservoir filled with drug/vaccine
- Hydrogel-forming patch applied to the skin
- Hydrogel microneedles swell upon coming into contact with the hydrophilic nature of the skin, releasing the drug/vaccine

Microarray Patches (MAPs)

Fig. 5. Representative images of different MAP concepts presented in the literature


**Microarray Patches (MAPs)**

<table>
<thead>
<tr>
<th>Type of MAP</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid MAPs</td>
<td>• Easy application and manufacturing</td>
<td>• Reliability and reproducibility of vaccine delivery</td>
<td>[55,61,71–73,154–162]</td>
</tr>
<tr>
<td></td>
<td>• Sharp tips with good mechanical strength</td>
<td>• Lack of precise dosing</td>
<td></td>
</tr>
<tr>
<td>Coated MAPs</td>
<td>• Minimal vaccine dosage needed</td>
<td>• Reformulation of the drug for different types of vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Allows for drug diffusion to deeper epidermal layers</td>
<td>• Limitations in coating the necessary vaccine dosage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dosage uniformity</td>
<td>• Vaccine stability during the drying and storage process</td>
<td>[51,64–68,74–77,79–85,88–95,97–106,146,163–172]</td>
</tr>
<tr>
<td></td>
<td>• Reduced sensitivity to humidity</td>
<td>• Retention of vaccine potency</td>
<td></td>
</tr>
<tr>
<td>Dissolvable MAPs</td>
<td>• Larger capacity to hold greater drug/vaccine payloads while ensuring a</td>
<td>• Vaccine compatibility and stability with solvent materials</td>
<td>[96,106–115,117–127,129–137,173–180]</td>
</tr>
<tr>
<td></td>
<td>precise and consistent release of dosage</td>
<td>• Effects of biodegradable materials on the mechanical strength of the MAPs</td>
<td></td>
</tr>
<tr>
<td>Hollow/porous MAPs</td>
<td>• Serves as a reservoir to allow for passive diffusion</td>
<td>• Potential of vaccine leakage, clogging of channel openings, and the</td>
<td>[60,141,148,181–188]</td>
</tr>
<tr>
<td></td>
<td>• Allows greater volume of liquid formulations to be delivered into the skin</td>
<td>collapse of microprojections due to their weak structure</td>
<td></td>
</tr>
<tr>
<td>Hydrogel-forming MAPs</td>
<td>• Uses a reservoir to store the drug/vaccine, enabling a higher</td>
<td>• Newly emerging technology that requires more research to understand the</td>
<td>[54,174,189–191]</td>
</tr>
<tr>
<td></td>
<td>volume/dosage to be administered</td>
<td>delivery efficacy, mechanism, safety, and other adverse effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Have not been thoroughly investigated in pre-clinically in animal models</td>
<td></td>
</tr>
</tbody>
</table>

Microarray Patches (MAPs)

Delivery Innovation: Measles–Rubella Microarray Patches
phase 2b proof-of-concept data expected May 2023

Results are published or anticipated for MR, Influenza, SARS-CoV-2, Hep B and JE in Phase 1, as well as Phase 2 studies for MR and SARS-CoV-2

WHO continues to enable and accelerate development through the Vaccine Innovation Prioritization Strategy

Available at: https://publichealth.jhu.edu/2023/game-changing-vaccine-developments
**Microneedle Vaccine Delivery Systems**

<table>
<thead>
<tr>
<th>Company</th>
<th>Type of Microneedle</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micron Biomedical</td>
<td>Dissolving microneedle</td>
<td>Inactivated rotavirus</td>
</tr>
<tr>
<td>3M (Kindeva)</td>
<td>Hollow microneedle</td>
<td>Cancer vaccines</td>
</tr>
<tr>
<td>BD Technologies (BS Soluvia)</td>
<td>Stainless steel microneedles</td>
<td>Influenza</td>
</tr>
<tr>
<td>Flugen</td>
<td>Metal microneedles</td>
<td>Influenza</td>
</tr>
<tr>
<td>Debiotech</td>
<td>Hollow microneedles</td>
<td>COVID-19</td>
</tr>
<tr>
<td>Verndari (Vaxipatch)</td>
<td>Stainless steel microneedle</td>
<td>Influenza, COVID-19</td>
</tr>
<tr>
<td>Nanopass (MicroJet™)</td>
<td>Silicon microneedles</td>
<td>Influenza, Polio, Varicella-Zoster, Cancers, Hepatitis B, COVID-19</td>
</tr>
<tr>
<td>BioSerenTach Inc.</td>
<td>Dissolving microneedles</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Sorrento therapeutics (Sofusa®)</td>
<td>Nanotopographical imprinted microneedles (coated)</td>
<td>Immuno-oncology</td>
</tr>
<tr>
<td>Vaxxas (Nanopatch™)</td>
<td>Coated microneedles array patch</td>
<td>Influenza, COVID-19</td>
</tr>
<tr>
<td>Quadmedicine</td>
<td>Dissolving microneedles</td>
<td>Influenza, Canine Influenza</td>
</tr>
<tr>
<td>Vaxess</td>
<td>Dissolving microneedles</td>
<td>Influenza, COVID-19, skin cancer</td>
</tr>
<tr>
<td>Raphas</td>
<td>Dissolving microneedles</td>
<td>HPV, Polio, Tdap, HBV, IPV, and Hepatitis B</td>
</tr>
</tbody>
</table>


www.mdpi.com/2072-666X/12/4/435
Jeremy Farrar, Director of the Wellcome Trust, said “No matter how great your idea, how exciting your new treatment, or how robust your science, it must be accepted by the people who stand to benefit from it. Vaccines, for example, are one of our most powerful public health tools, and we need people to have confidence in them if they are to be most effective.”