What’s new in vaccine research and development

Manika Suryadevara, MD
Associate Professor of Pediatrics
SUNY Upstate Medical University
Syracuse, NY

Disclosure

I am the principal investigator for clinical trials sponsored by Janssen and Hoffman-La Roche Ltd.
Objectives

- Attendees will list the steps required and general timeline needed to move a preclinical vaccine idea to a vaccine that is available for widespread use.

During this talk...

- Describe the stages of vaccine development
- Review vaccines currently in the pipeline
- Discuss novel immunization strategies
# Impact of vaccines on infectious disease morbidity in the United States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-vaccine Morbidity</th>
<th>Recent reported cases in US</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Polio</td>
<td>16,316</td>
<td>1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>187</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>H. Flu b</td>
<td>20,000</td>
<td>31</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>26</td>
<td>96%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>28,639</td>
<td>86%</td>
</tr>
</tbody>
</table>

## Vaccines licensed for use in the US

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Disease/Pathogen</th>
<th>Disease/Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Japanese encephalitis virus</td>
<td>Rotavirus</td>
</tr>
<tr>
<td>Diphtheria, tetanus, acellular pertussis</td>
<td>Measles, mumps, rubella</td>
<td>Smallpox</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td>Meningococcal ACWY</td>
<td>Typhoid</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Meningococcal B</td>
<td>Varicella</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Pneumococcal</td>
<td>Yellow Fever</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Polio</td>
<td>Zoster</td>
</tr>
<tr>
<td>Influenza</td>
<td>Rabies</td>
<td>Cholera</td>
</tr>
</tbody>
</table>

## Vaccine Development
Vaccine Development

- Highly regulated process
- Can take 10-15 years from concept to recommendation
- Most vaccine candidates do not make it past pre-clinical or early clinical trials (phase I)

Vaccine Development Timeline

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Years to approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>25-30</td>
</tr>
<tr>
<td>Live attenuated influenza vaccine</td>
<td>25-30</td>
</tr>
<tr>
<td>HPV*</td>
<td>14-16</td>
</tr>
<tr>
<td>Rotavirus*</td>
<td>14-16</td>
</tr>
<tr>
<td>Pediatric combination vaccines</td>
<td>10-12</td>
</tr>
</tbody>
</table>

* Excluding early pre-clinical work

Drivers of vaccine development

- Limited-use product
- 10-15 years until marketing
  - Uncertain demand in market
  - Incorporation in immunization program
    - Clinical
    - Economic

Demand for vaccine in market

Technically feasible

Vaccine development

Clinical development
- Vaccine impact
- Safety, efficacy, immunogenicity
- Phase I, II, III trials

Process development
- Vaccine preparation
- Vaccine lots
- Manufacturing methods

Assay development
- Testing methods:
  - Purity
  - Stability
  - Potency
- Assays for immunologic endpoints
Vaccine Development

Pre-clinical Phase I Phase II Phase III File Phase IV

1-10 years 2-3 years 2-5 years

Pre-clinical phase

Vaccine concept
Identification of antigens
Lab assays, animal models
Pre-clinical phase

IND Application

- Manufacturing process
- Vaccine composition
- Vaccine safety
- Vaccine potency
- Vaccine efficacy
- Vaccine purity

Pre-clinical data
Proposed clinical trials plan

Phase I clinical trials

Small studies
- ~50
- Healthy adults
- Low risk for infection
- Short-term

Outcomes
- Primary
- Safety
- Secondary
- Immunogenicity
- Vaccine dosing
Phase I example

- Study vaccine: 12-17 month olds, sero-positive
- Dose escalations with safety assessments

- Primary outcome: Safety
- Next step: study vaccine in sero-negative infants

Phase II clinical trials

<table>
<thead>
<tr>
<th>Longer, larger</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 2 years</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>~1,000 subjects</td>
<td>Immunogenicity</td>
</tr>
<tr>
<td>At-risk for infection</td>
<td>Expanded data</td>
</tr>
<tr>
<td>Double-blinded, placebo-controlled, randomized</td>
<td>Safety</td>
</tr>
<tr>
<td></td>
<td>Vaccine dosing</td>
</tr>
</tbody>
</table>
Phase II Example

- Study monoclonal antibody in healthy pre-term infants
- Early assessment of reduction in medically attended respiratory infections

Phase III clinical trials

<table>
<thead>
<tr>
<th>Large-scale</th>
<th>Assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1000s of subjects</td>
<td>• Safety</td>
</tr>
<tr>
<td>• At risk for infection</td>
<td>• Efficacy</td>
</tr>
<tr>
<td>• Lasts several years</td>
<td>• Immunogenicity</td>
</tr>
<tr>
<td>• Randomized, placebo-controlled, blinded</td>
<td>• Clinical end-points</td>
</tr>
<tr>
<td></td>
<td>• Immunologic end-points</td>
</tr>
</tbody>
</table>
Phase III Example

- Study vaccine: 3rd trimester pregnant women
  - Immunologic endpoints
    - Pregnant women
    - Cord blood
    - Newborns
  - Clinical endpoints – infants for 2 years
  - Safety data collected

File for license

<table>
<thead>
<tr>
<th>Biologics License Application (BLA) submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit safety/efficacy to FDA</td>
</tr>
<tr>
<td>Vaccines and Related Biologic Product Advisory Committee</td>
</tr>
<tr>
<td>Review data with VRBPAC</td>
</tr>
<tr>
<td>Pre-approval inspection of vaccine production</td>
</tr>
<tr>
<td>18-24 months</td>
</tr>
</tbody>
</table>
**File for license**

**FDA**
- Decides on licensure
- Restricted to study population

**ACIP**
- Reviews data in context of current needs
- Makes vaccine recommendation

**Discordant Examples**

<table>
<thead>
<tr>
<th>FDA label indication</th>
<th>ACIP recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap – one dose and done</td>
<td>Tdap every pregnancy</td>
</tr>
<tr>
<td>Tdap for people aged 10-64 years</td>
<td>Tdap for all 7 years and older</td>
</tr>
<tr>
<td>Quadrivalent meningococcal – one dose</td>
<td>Quad mening – 2 doses for all teens</td>
</tr>
<tr>
<td>MenB 10-24 years of age</td>
<td>MenB 10 years and older for those at risk</td>
</tr>
<tr>
<td>Influenza vaccine not specifically licensed during pregnancy</td>
<td>Influenza vaccine during pregnancy</td>
</tr>
</tbody>
</table>
Phase IV

- Post-licensure surveillance
  - Safety surveillance
    - VAERS, Vaccine Safety Data Link, manufacturer reports
    - Case-controlled studies when ‘Red Flags’ appear
    - Look for rare adverse events
  - Long-term efficacy evaluation
    - During outbreaks, ongoing epidemiologic data collection
  - Manufacturer production activities

Vaccine Development

- Cost of developing new vaccine
  - $231 million in 1991 → $800 million in 2010
  - Research and development costs of failed products
  - Post-licensure clinical studies
  - Improvements in manufacturing processes
Vaccine Development

- Government agencies
  - CDC, FDA, DOD, USAID, NIH
- Private Vaccine Companies
- NGO
  - Gates Foundation, PATH

Contributions to Vaccine R&D

- Highly regulated
- Single set of rules applied to all vaccines
- Regulations of manufacturing process
- Regulations of clinical trials
- Complicated, costly, with more failures than successes
Vaccines in the pipeline:

- Clinicaltrials.gov
  - Search: vaccine
  - 6,670 registered vaccine trials
  - 1,100 open vaccine trials
  - 642 trials actively recruiting
Phase 1 clinical trials

- Universal flu vaccine
- Group B strep
- Meningococcal ABCWY
- RSV
- Ebola
- MERS-CoV

Phase 2 clinical trials

- Ebola
- Pneumococcus
- Hepatitis C
- Malaria
- Meningococcal ABCWY
- Shigella
- Hexavalent peds
- Tuberculosis
- RSV
- HIV
- Universal flu
- CMV
- Rabies
- Tdap
Phase 3 clinical trials

- Pneumococcus
- Rotavirus
- MMR
- Ebola
- Flu
- RSV
- Men ABCWY
- VZV
- C. diff

Novel immunization strategies

- Improving currently available vaccines
- Developing vaccines for new diseases
- Reduction of antimicrobial resistance
Influenza vaccines

Influenza virus

Virus attachment to host cell

Virus entry into host cell

cdc.gov
Types A, B, C
- A, B: most of human disease
- C: uncommonly causes human disease

Influenza A
- Sub-typed by HA and N types
- Seasonal epidemics; pandemics

Vaccination is most effective method for disease prevention

Current influenza vaccine production

- IIV: intradermal, IM
- A (H1N1)
- A (H3N2)
- B

- Trivalent, quadrivalent
- LAIV: intranasal

- Cell-based
- Egg-based
- Recombinant
Current influenza vaccine production

CDC and WHO provide candidate vaccine viruses

- Egg-based: Virus injected into fertilized hen’s egg
- Cell-based: Virus inoculated into mammalian cells
- Recombinant: HA protein isolated from wild-type virus and combined with proteins to grow in insect cells

- incubate for virus replication
- virus containing fluid harvested
- virus inactivated and FDA testing, approval, shipment

Limitations with current production

- Vaccine efficacy ~30-50%
- Most effective when strain antigens match circulating viruses
- Circulating strains change yearly
- Do not protect against pandemics
Influenza vaccines to come

- NIH leading research for *universal* flu vaccine

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<th>Goals</th>
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<tbody>
<tr>
<td>At least 75% effective</td>
</tr>
<tr>
<td>Protects against multiple types of influenza A (<em>pandemic strains included</em>)</td>
</tr>
<tr>
<td>Duration over a year</td>
</tr>
<tr>
<td>Suitable for all age groups</td>
</tr>
</tbody>
</table>

www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research

Universal influenza vaccine

- Current vaccines induce antibody to HA head
- Changes frequently

Universal influenza vaccine

- More conserved
- Vaccine to induce antibody to stalk


Universal influenza vaccine

- More conserved
- Vaccine to induce antibody to stalk

nanoparticles

4 H subtypes into one vaccine

DNA-based vaccine “prime” [phase 1, 2]

M-001: antigenic peptides from many strains [phase 2]

RSV vaccines

- F glycoprotein
  - Mediates fusion reaction → delivery of virus capsid core contents into cell
  - Disrupting activity would
    - reduce virus entry into cell
    - protect host from infection
  - Highly conserved among strains
RSV vaccine – target populations

- Infants
  - Active immunization
  - Passive immunization
- Pregnant moms –
  - RSV Ab efficiently transferred across placenta
  - High cord blood RSV Ab levels lower incidence of severe RSV LRTI
  - Passive immunization

- Formalin inactivated-RSV vaccine
- Infants 2-7 months of age
- Enhanced disease
  - Hospitalizations: 80% of vaccinated vs 5% placebo
  - 2 deaths from RSV infection among vaccinated
- Thought to be due to
  - Ab produced: non-neutralizing and did not inhibit fusion
  - Inflammatory response
### Live Attenuated

- Codegenix
- Novel Biosciences
- Acroloc Healthcare

### Whole Inactivated

- Novavax

### Particle based

#### Subunit

- AgBio
- Fossbiotec
- Hypertech
- Genetic 
- BioTechnologies
- Genentech
- Biomerieux
- Merck
- Novartis
- Pfizer
- SmithKline
- Wyeth

#### Nucleic Acid

- Couvant
- Genscript
- Genstar Pharmaceuticals

### Subunit Vectors

- Invitrogen
- Reseller
- Biogenes
- Covance
- Genentech
- Biomerieux
- Roche
- University of Cambridge
- University of Washington
- University of Pennsylvania
- University of Minnesota
- Medimmune

### Immuno prophylaxis

- Merck
- Genentech
- Biogenes
- Covance
- Medimmune

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**RSV Nanoparticle vaccine**

**Spodoptera frugiperda** (Fall armyworm)

- Only infects insects
- Engineer to carry genes of interest
- Used to infect Sf9 cells to efficiently produce desired protein

1. ID genetic sequence of RSV F protein
2. Clone gene into baculovirus
3. Engineered baculovirus infects the Sf9 cells
4. RSV F proteins produced
5. Transported to surface, extracted, purified
Ad vector-based RSV vaccine

- Safe and inexpensive
- High capacity
  - Infect cells
  - Express encoded antigens
  - Induce immune response
- Adenovirus type 5
  - Most common human Adenovirus serotype
  - 30% + Ad Ab → less immunogenic

- Chimpanzee adenovirus
  - Related to human adenovirus
  - Low neutralizing antibodies in human population

Fusion process between the RSV envelope and cellular membrane.

Fusion process between the RSV envelope and cellular membrane.

Pre-fusion F vs Post-fusion F
most vaccines target post-fusion F
Pre-fusion F induces more robust response with greater neutralizing potential

Monoclonal Antibodies

- Passive protection
- Palivizumab
  - Prevention of RSV
  - Licensed in 1998
  - Monthly injections during RSV season
Monoclonal Antibodies -- YTE

- monoclonal antibody
- Targets prefusion F
- YTE technology

YTE technology substitutes 3 amino acids in the Fc region of IgG.

Use of vaccines to reduce antimicrobial resistance (AMR)
Anti-microbial resistance

Hard to treat infection

Longer hospital stays

Higher medical costs

Increased mortality rates

Vaccinations
→ disease prevention
→ reduced antibiotic use

https://www.nature.com/articles/nmicrobiol2016187/figures/1
Vaccines to reduce AMR

Jansen et al, Nat Med. 2018; 24: 10-19

Vaccines to reduce AMR

- Pneumococcal vaccine
- Hib vaccine
- Flu vaccine

Potential of vaccines targeting other viruses (RSV)
WHO priority list: new abx for AMR

Priority 1 (critical)
- Acinetobacter
- Pseudomonas
- Enterobacter

Priority 2 (high)
- Enterococcus
- Staphylococcus
- H. Pylori
- Salmonella
- N. gonorrhea

Priority 3 (medium)
- S. pneumo
- Hib
- Shigella

Tacconelli et al. Lancet Infectious Diseases; 2018; 18: 318-27

WHO priority list: new abx for AMR

Priority 1 (critical)
- Acinetobacter
- Pseudomonas
- Enterobacteriaceae

Priority 2 (high)
- Enterococcus
- Staphylococcus
- H. Pylori
- Salmonella
- N. gonorrhea

Priority 3 (medium)
- S. pneumo
- Hib
- Shigella

Existing vaccines
Pipeline vaccines

Multi-drug resistant tuberculosis
Group B streptococcus
Respiratory syncytial virus
Clostridium difficile

Jansen et al, Nat Med. 2018; 24: 10-19
Tacconelli et al. Lancet Infectious Diseases; 2018; 18: 318-27
Rigorous regulations in vaccine development
- Significant amount of time and money to ensure safe and effective vaccines
- Novel vaccine strategies are being developed to improve disease prevention
- New vaccines are becoming available in the US and worldwide