Welcome to ACDRS Webinar Series

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VACCINE DEVELOPMENT

The Challenges (without and with a pandemic)

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What is a vaccine designed to do?

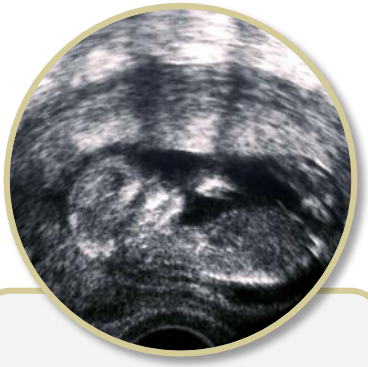
- Prime the adaptive immune system to rapidly respond to an infection with the aim of preventing or mitigating the associated clinical disease.
  - A vaccine’s primary objective is NOT necessarily to prevent infection.
- The adaptive immune system is designed to “learn” from previous infectious encounters.
- A vaccine essentially takes the place of the initial “teaching” encounter.

What form does a vaccine take?

- Live, attenuated version of the wild-type pathogen
- Chemically inactivated version of the pathogen
- Chemically inactivated version of a pathogen-derived toxin
- Recombinantly expressed protein
  - Mammalian cell culture
  - Yeast
  - Insect cells
- Free or conjugated polysaccharides

- Genetically modified viral or bacterial “vectors” expressing the vaccine target protein
- DNA or RNA expressing the vaccine target protein

VACCINES FOR HUMAN INFECTIOUS DISEASES



NEONATAL

Hepatitis B

PEDIATRIC

Polio
Diphtheria
Tetanus
Pertussis
Measles
Mumps
Rubella
Varicella
Rotavirus
Influenza
Hib
13v Pneumococcal conjugate
Hepatitis B
Hepatitis A
TB (BCG)

ADOLESCENT

Papillomavirus
Influenza
Meningococcal A, C, Y, W
Meningococcal B

ADULT

Influenza
Zoster
13v Pneumococcal conjugate

Vaccine constituents and the nature of the immune response

- **An effective vaccine requires:**
  1. **The ability to co-engage the innate immune response in conjunction with the adaptive response**

- **To do this, a vaccine must contain:**
- The adaptive immune system's effective target or antigen
  - Usually a defined element of the pathogen's structure (protein, polysaccharide)

- A stimulator of the innate immune response (the "danger signal")
  - Either an endogenous part of the pathogen/vaccine vector or
  - An adjuvant (e.g., alum, oil-in-water, quil A, bacterial components, CpG)

The method and timing of vaccine delivery is critical

- **<u>An effective vaccine requires</u>:**
  1. **The initial co-elicitation of the innate response in conjunction with the adaptive response**
  2. **The establishment of the adaptive response "memory"**

- Requires both initial "priming" and subsequent "boosting"

- Fully replicating vaccines (live attenuated or recombinant) may be delivered only once

- Non-replicating vaccines typically require:
  - Two closely spaced priming administrations
  - One or multiple widely spaced booster administrations

Vaccine development challenges without the concerns of a pandemic

- Vaccines are primarily designed for use in healthy individuals
  - Safety considerations are paramount
- Often the nature and target of the effective immune response is unknown or (at least) uncertain
- The physical characteristics of the vaccine and/or its formulation responsible for eliciting the protective immune response is never 100% certain
- Immune responses and efficacy using pre-clinical animal models cannot be extrapolated to humans with 100% certainty
- **Vaccine development requires a high level of control, characterization, and measurement**

Key elements of the vaccine development process

- Understanding of the nature of the infection's pathophysiology and the nature of the potentially protective immune response
  - Development of "relevant" animal models
  - Development of laboratory assays that will quantitatively and robustly measure the immune responses
- Designing the vaccine and formulation that will be most likely to elicit the desired memory immune response
  - Antigen structure/valency
  - Formulation for stability
  - Adjuvant selection
- Selecting the antigen expression systems and adjuvant formulations
  - Likely to be tolerable, safe, and immunogenic in humans
  - Scalable to productive manufacturing scale (facilities, raw materials, personnel)

Clinical evaluation occurs in a careful and controlled fashion

- Phase 1 (tens of subjects)
  - Initial definition of dosage (tolerability and immunogenicity) in healthy low-risk volunteers
  - Can use “experimental” forms of the vaccine
- Phase 2 (hundreds of subjects)
  - Confirmation of dosage in larger numbers and in at-risk volunteers
  - Establishment of dosage in “special” at-risk populations
  - Use vaccine representative of the final manufacturing process and formulation
- Phase 3 (thousands to tens of thousands of subjects)
  - Safety and efficacy in the at-risk population
  - Must use vaccine representative of the final manufacturing process/formulation and manufacturing scale
  - Demonstration of manufacturing consistency
  - Definition of critical quality attributes and associated limits

Parallel development risks

- Correct definition of the protective immune response
- Development of qualified assays to consistently measure the response
- Selection of a production process that is scalable
  - Scaling production and establishing a manufacturing network
- Definition of the vaccine's quality attributes that are most likely to be associated with efficacy
- Development of qualified assays to consistently measure the attributes
- Tolerance limits of the critical quality attributes
  - Impact on manufacturing consistency
  - Impact on stability and storage/transport/use
- Balance between immunogenicity and tolerability/safety in humans
- Efficacy and duration of efficacy

- **Highly regulated and deliberate development process that represents substantial financial investment and risk**
  - **Many years (5-10), large numbers of experienced personnel, and large investments (100s of millions to > billion)**

Regulatory control and interactions

- As with any pharmaceutical product, vaccine development is high regulated:
  - Pre-clinical safety studies (including reproductive toxicology)
  - Pre-clinical immunogenicity and “efficacy” assessments
  - Clinical study design and execution
  - Clinical and quality assay design, qualification, and validation
  - Establishment of release and stability criteria
  - Requirements for clinical evaluations in “special” populations and circumstances
    - Relevant age and at-risk groups
    - Concomitant vaccine usage
    - Immunocompromised
    - Pregnant women
  - Manufacturing consistency (across sites and time)
  - Post-approval requirements

  - Multiple agencies:
    - FDA, EMA, MHRA, CFDA, etc.
    - WHO PQ

Vaccine development in the time of a pandemic

- The uncertainties and risks of the development process are greatly amplified given the time constraints
- Mitigation is managed through a combination of luck and large at-risk financial investments
- Small and inexperienced vaccine developers can only afford limited risk
- Large and experienced multi-national developers also need to mitigate risk

COVID-specific risks

- Assumption regarding the nature of the protective immune response based on studies of related coronaviruses and on natural history studies of SARS-CoV2.
- Assumption regarding the preferred structure of the target antigen (the CoV2 spike protein) and method of presentation/production
- Assumption regarding the preferred adjuvant formulations
- Assumption regarding the manufacturability and scalability of the selected production methods
- Assumption regarding eventual efficacy, particularly in high at-risk populations
- Requirement to develop a vaccine within 12-18 months

Risk mitigations

- Parallel research studies to understand the nature of the protective immune response and development of possibly predictive animal models

- National and international investments into at-risk vaccine early development, manufacturing scalability, and large accelerated clinical studies

  - BARDA (U.S.): Biomedical Advanced Research and Development Authority
  - CEPI Alliance: Coalition for Epidemic Preparedness Innovation
    - COVAX Alliance: CEPI/WHO/GAVI

    - Provision of “push” and “pull” funding in addition to manufacturing networks and large clinical study capabilities

  - Regulatory coordination and alignment

Engaging multiple approaches in parallel

- mRNA or DNA antigen delivery
- Viral and bacterial (non-replicating and replicating) vaccine vectors
  - Non-replicating chimpanzee adenovirus virus vectors
  - Non-replicating human adenovirus vectors
  - Replicating measles virus vectors
  - Replicating vesicular stomatitis virus (VSV) vectors
- Recombinantly expressed protein with multiple adjuvant formulations
  - Insect cell expression of VLPs
  - Mammalian cell expression of stabilized antigens
  - Multiple adjuvant formulations

- Inactivated intact SARS-COV2

Considerations for Phase 3 evaluation of COVID vaccines: Demonstration of safety and efficacy

- International multi-site encompassing 30,000 to 60,000 subjects

- Endpoint definition of clinical disease: mild/moderate/severe?
- Statistical definition of vaccine efficacy (VE):
  - Target efficacy of 50-60% with exclusion of the 95% lower bound of 30%
- Demonstration of immunogenicity (efficacy?) in older adults and at-risk populations
- Sufficient safety/tolerability observations (numbers and time)

- Interim analyses to support “emergency use authorization” and/or conditional approval
  - Maintenance of study until completion

COVID Vaccine Distribution and Use: Uncertainties

- Lack of truly global regulatory harmonization
- Import/export restrictions
- Indemnification
- Cost of acquisition and use
- Transport capacity
- (Ultra) cold-chain requirements
- Administration and tracking

Lessons for the future

- Develop vaccine delivery platforms that can be easily adapted
- Maintain sufficient manufacturing capacity suitable for the available platforms
- Maintain sufficient fill/finish capacity
- Globally increase the number of organizations with vaccine research, development, and manufacturing capability
- Design prospective streamlined and coordinated regulatory pathways
- Expand the capabilities of international funding organizations

THANK YOU