ADVAC
ADVANCED COURSE OF VACCINOLOGY

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Will the success of mRNA vaccine development platforms for COVID-19 lead to new platforms for old vaccines?

Chair: Martin Friede, World Health Organization and Member of the ADVAC Scientific Committee

Presenters: **Barney Graham,** former Deputy Director of the NIAID Vaccine Research Center, National Institute of Health, USA

The Immunological benefits of mRNA and potential applications

Philip Krause, Deputy Director of the Office of Vaccines Research and Review, Food & Drug Administration, USA

Regulatory approaches: Issues and challenges, and questions to be asked by regulators

All participants can ask questions and/or make comments. To ask a question or comment, you can signal your interest in writing by sending a message with your question/comments to “all participants” in the chat box. You will then be invited in turn to ask your question live and while doing so are kindly reminded to unmute your microphone and activate your video.

We apologize in advance for all questions that cannot be answered live due to lack of time. We will keep track of questions sent in writing and for those that have not been addressed, we will try to secure an answer that will be sent via email to all registered participants.

Disclaimer & COI

- No conflicts to report
- This talk presents my own personal opinions, which are not necessarily those of any organization

Regulatory considerations

- Regulations have the force of law
- Regulatory decisions should be based on good science
- For vaccine development, this implies that study designs:
  - Will provide scientifically valid results, e.g., studies are adequate and well-controlled
  - Conforms to ethical and human subjects protection standards
  - Likely will yield outcomes that could ultimately support broader availability of vaccine, ideally via licensure
- Implies the importance of early and frequent conversations with regulators, to help assure that study designs and objectives will meet goals

What are potential advantages of mRNA vaccines

- Relatively easy to make and adjust
- COVID experience may streamline movement into phase 1
- High antibody titers
- Higher potential likelihood of efficacy may support more at-risk development decisions
- Some cell-mediated responses– though possibly not always to the most important antigens for cell-mediated immunity

What are potential disadvantages of mRNA vaccines?

- Questions about durability of protection
  - Appropriate regimen and duration of protection isn't yet known
    - Would we contemplate a 2-dose mRNA vaccine regimen for influenza?
    - Pediatric regimens aren't clear yet
  - Role of original antigenic sin not yet well defined
  - How certain can we be that we have the right antigens?
- Safety
  - Possible autoimmune risks, especially with many doses
    - Myocarditis?
  - Other potential safety risks associated with frequent re-exposure to the same modality
  - Heightened concern for pediatric vaccines

Other considerations

- Lipid nanoparticles likely play a critical role in immune response.
- Could adjuvants further increase immune responses or duration of protection?

“Old vaccines”

- Is there a market for a replacement?
- Is an mRNA vaccine likely to work against the pathogen targeted by the old vaccine?

US licensed bacterial vaccines

Target	Type
Anthrax	Adsorbed
BCG	Live
Cholera live	Live
D, T, and or P	Adsorbed
Haemophilus b	Conjugate
Meningococcal (A,C,Y,W-135)	Conjugate
Mening Group B	Recombinant
Mening (A,C,Y,W-135)	Polysaccharide
Plague	Inactivated
Pneumococcal	Conjugate
Pneumococcal	Polysaccharide
Typhoid	Live
Typhoid	Polysaccharide

US licensed viral vaccines

Target	Type
Adenovirus	Live
Covid mRNA	
Dengue	Live
Hepatitis B	Recombinant
Ebola Zaire	Live
Hepatitis A	Inactivated
HPV	Recombinant
Influenza	Inactivated
Influenza	Live
Influenza	Recombinant
Japanese Encephalitis Virus	Inactivated
Measles, Mumps, Rubella, Varicella	Live

Target	Type
Poliovirus	Inactivated
Rabies	Inactivated
Rotavirus	Live
Smallpox, Monkeypox	Live or non-replicating
Tick borne encephalitis	Inactivated
Yellow fever	Live

Vaccine Licensure: Pathways to demonstrate efficacy

- "Traditional" Approval
- Accelerated Approval
- "Animal Rule"

Clinical demonstration of safety required for all pathways

Considers nature of the product, intended use, and severity of the disease to be prevented

Demonstration of effectiveness required for all pathways; differences in approach among pathways

Accelerated Approval and Animal Rule-- specific "eligibility" criteria and associated requirements

"Traditional" Approval

Pre-licensure clinical studies provide evidence of effectiveness based on:

- Protection against clinical disease
- Immunologic response, in some cases
  - scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
  - facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease

Accelerated Approval

21 CFR 601.40 and 601.41

- *Scope:* Products studied for safety and effectiveness in treating serious or life-threatening illnesses AND that provide meaningful therapeutic benefit over existing treatments
- Approval may be based on adequate, well-controlled clinical trials establishing an effect on **a surrogate endpoint that is reasonably likely…to predict clinical benefit**…
- Because such a surrogate endpoint may be difficult to identify based on proposed mechanisms for secondary effects, this pathway might not be feasible for secondary effect-based licensure
- Requirement to verify clinical benefit; required post-marketing studies:
  - usually underway at time of approval
  - must be adequate and well-controlled
  - must be conducted with due diligence

"Animal Rule"

21 CFR 601.90-91

- *Scope:*
- Products that have been studied for safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances
- Other requirements include "There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product" which may preclude animal rule use for secondary effects without further research.
- Human efficacy studies cannot be conducted:
  - unethical to deliberately expose healthy humans
  - field trials after accidental or hostile exposure not feasible
- **Not applicable if product can be approved based on other efficacy standards** (i.e. "traditional" approval or accelerated approval)
- Requirement for follow-up studies (when feasible) to verify benefit

Influenza vaccines guidance: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

- Accelerated approval IN PLACEBO CONTROLLED IMMUNOGENICITY STUDIES
- Specific criteria must be met for accelerated approval eligibility

including supply considerations

  - Non-inferiority vs. licensed seasonal influenza vaccine
  - For adults <65 and pediatrics:
    - HI LB seroconversion≥40% and ≥ 1:40 ≥ 70%
  - For adults >=65
    - HI LB seroconversion ≥ 30% AND ≥ 1:40 ≥ 60%

Previously used surrogate markers for vaccines

Disease or Use	Patient Population	Surrogate Endpoint	Type of approval appropriate for	Drug mechanism of action
Anthrax vaccine	Persons at high risk of exposure to anthrax	Anti-protective antigen antibody response	Traditional	Induction of immunity
Hepatitis A (Hep A) vaccine	Persons to be immunized against Hep A	Anti-Hep A antigen antibody	Traditional	Induction of immunity
Hepatitis B (Hep B) vaccine	Persons to be immunized against Hep B	Anti-Hep B antigen antibody	Traditional	Induction of immunity
Human Papillomavirus	Persons (18 through 45 years of age) to be immunized against human papillomavirus	Cervical intraepithelial neoplasia	Traditional	Induction of immunity
Influenza vaccine	Persons to be immunized against influenza	Hemagglutination inhibition antibody	Accelerated	Induction of immunity
Invasive pneumococcal disease	Patients with invasive pneumococcal disease	Opsonophagocytosis assay titers	Traditional	Induction of immunity
Japanese encephalitis vaccine	Persons to be immunized against Japanese encephalitis	Neutralizing antibody	Traditional	Induction of immunity

Previously used surrogate markers for vaccines (2)

Disease or Use	Patient Population	Surrogate Endpoint	Type of approval appropriate for	Drug mechanism of action
Meningococcal (serogroups A, C, Y, W) meningitis vaccine	Persons to be immunized against meningococcal meningitis	Serum bactericidal antibody	Traditional	Induction of Immunity
Meningococcal Group B vaccine	Persons (18 through 25 years of age) to be immunized against meningococcal meningitis	Serum bactericidal antibody	Traditional	Induction of immunity
Monkeypox vaccine	Persons to be immunized against monkeypox	Vaccinia-neutralizing antibody	Traditional	Induction of immunity
Pertussis (in combination vaccines)	Persons (18 through 64 years of age) to be immunized against pertussis	Serum antibody concentrations	Traditional	Induction of immunity
Pneumococcal conjugate vaccine	Persons (≥ 50 years of age) to be immunized against pneumonia and invasive disease	Opsonophagocytic antibody response	Accelerated	Induction of immunity
Polio vaccine	Persons to be immunized against polio	Neutralizing antibody response	Traditional	Induction of immunity

Previously used surrogate markers for vaccines (3)

Disease or Use	Patient Population	Surrogate Endpoint	Type of approval appropriate for	Drug mechanism of action
Rabies Vaccine	Persons to be immunized against rabies	Neutralizing antibody	Traditional	Induction of immunity
Smallpox vaccine	Persons to be immunized against smallpox	Vaccinia-neutralizing antibody	Traditional	Induction of immunity
Smallpox vaccine	Persons to be immunized against smallpox	Vaccination site take reaction (replicating smallpox vaccines only)	Traditional	Induction of immunity
Tetanus vaccine	Persons to be immunized against tetanus	Anti-tetanus toxoid antibody	Traditional	Induction of immunity
Yellow fever vaccine	Persons to be immunized against yellow fever	Neutralizing antibody	Traditional	Induction of immunity

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Conclusions

- For the old vaccines, diseases that can be prevented by recombinant vaccines may be most amenable as mRNA vaccine targets
- For many pathogens, mRNA vaccines could potentially be evaluated via non-inferior immune response to existing vaccines, indicating reasonable likelihood of clinical benefit (subject to agreement with regulators for each specific pathogen)
- If made available under accelerated approval, post-marketing studies would need to confirm benefit
- Influenza is fairly well-matched to known strengths of mRNA vaccines