

# Maternal Immunization Challenges & Opportunities:

Perspective of Vaccine Developers & Manufacturers

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# Overview of Presentation

- **Maternal Immunization Landscape**
- **Clinical Development Challenges**
- **Policy Challenges**
- **Summary of Key Points**

# Maternal Immunization Landscape

- **A decade ago, routine maternal immunization seemed improbable.**
- **Through the work of CDC, NVPO, ACOG and the stakeholder community, a maternal immunization platform has been established.**
  - Recommendations for use and uptake of flu & Tdap vaccines in pregnant women have changed the landscape drastically.
  - Programs that encourage uptake of vaccines by OB/GYNs help reinforce the value of vaccines in pregnant women.
  - NVAC and ACCV have undertaken thorough reviews of VICP liability protection for maternal immunizations and made recommendations.

# Maternal Immunization Landscape

- **Assessment of benefit/risk is unique for maternal immunization.**
  - In some cases, a novel vaccine could be administered to the pregnant woman to protect the infant only and not the mother.
  - In other instances, there may be direct benefit to the woman and the infant.
  - If no benefit accrues to the woman, vaccine candidates must present the least possible risk to her while achieving the research objective.

# Maternal Immunization Landscape

- **Companies are now developing novel vaccines specifically intended for use in pregnant women, and are also conducting post-licensure development programs designed to support maternal immunization recommendations.**
- **Continuing the progress made thus far depends on:**
  - Continued growth in vaccination rates for flu & Tdap in pregnant women to demonstrate viable interest;
  - Support of vaccine companies as they engage in complex clinical trials;
  - Clarity related to liability coverage that will be critical for developers and providers; and
  - Clarity regarding the standards for clinical evidence that leads to timely ACIP recommendations.

# **Clinical Development Challenges for Current & New Vaccines**

# Clinical Trial Data Generation for Existing Vaccines

- **Approaches to data generation are needed that reinforce public health value.**
  - Efficacy data that supports an existing ACIP recommendation could be generated.
  - The concern is that this data may not be considered robust enough by FDA to support an additional indication because of lack of proper controls.
- **As pre-licensure studies in pregnant women were not conducted, clarity is needed from FDA on the acceptability of effectiveness studies to support an indication, given universal flu and Tdap recommendations.**
  - This could help reconcile data that is relevant for both FDA indications and ACIP recommendations.
    - What data is needed to support an indication for pregnant women? For infants?
    - Is there a way to design clinical trials to collect data that best supports public health goals? E.g. data generation to support Tdap's recommendation for use in pregnant women.
    - Is there data that could be collected by manufacturers and included in the package insert that would help support clinical decision-making?

# Clinical Trial Design Challenges

## ■ Determination of efficacy endpoints

- Conducting clinical trials in this population is relatively new territory for companies.
- Depending on the risk assessment, efficacy will need to be measured separately in two subjects (mother and child) and this may be required for several months post-vaccination and post-birth.
- Companies must work closely with the FDA to determine the best measures of efficacy.
- For some diseases immunogenicity markers may be more feasible and appropriate than measuring actual clinical efficacy outcomes.
- The choice of efficacy measure affects both the approval process and the ACIP recommendation process.

# Clinical Trial Design Challenges cont'd

- **Global epidemiology and incidence would have a significant impact on size and location of a clinical outcome efficacy trial**
  - Disease incidence may differ significantly between developed and developing countries. The level of healthcare infrastructure surrounding pregnant women and infants will also differ.
  - Given this, developers must select clinical locations across a range of countries with variable regulatory requirements, trial standards and access to post-market surveillance systems to conduct an outcome study.
  - In countries with lower incidence (U.S.), trial sizes could be ***significantly large*** and lengthy to achieve the required cases to demonstrate efficacy.
- **Assessment of safety in two distinct populations**
  - Women and infants will need to be followed after birth for safety, which may be especially challenging in developing countries with limited infrastructure.
  - Background rates are needed for certain outcomes in pregnant women and infants to accurately assess AEs.
  - Case definitions are needed as well as validated developmental assessments for newborns.

# Clinical Trial Enrollment Issues

## ■ Pregnant women are a special population

- Heightened awareness of health implications of maternal exposures, including vaccines.
- Potential use of novel adjuvants in pregnant women may require an additional risk/benefit discussion between the study investigator and the patient.
- More likely to be risk-averse which could translate into stronger resistance to participate in a clinical trial.

## ■ Strong support needed from key medical societies: ACOG, AAFP, AAP, ACP

- Scientific realities must be separated from commonly-held misconceptions to better overcome any misinformation held by potential enrollees.
- Importance of providing accurate information endorsed by organizations like ACOG.

## ■ OB/GYNs as vaccine investigators

- To date, this is not a traditional role for OB/GYNs.

 Any provider hesitancy will strongly influence the pregnant woman's decision to participate.

# Ethical & Other Considerations

## ■ IRBs are especially cautious about this population

- Requirements for additional safeguards and procedures in a healthy yet uniquely vulnerable population.
  - Exclusion/inclusion criteria of healthy women may be hard to define.
- Informed consent must account for the mother & child.
  - Must define the consent requirements on behalf of the mother and child, and fully inform the appropriate persons about potential impacts on both mother and child.

## ■ Companies do not have specific liability protections under IND

- There have been past instances of clinical trial participants suing vaccine developers during an ongoing clinical trial.
- Liability concerns may be higher for maternal immunization considering the heightened risk aversion in this special population and high rates of baseline SAEs in the peripartum period.

# Post-Marketing Requirements

- **Uncertainty about what post-marketing requirements for safety will look like.**
  - Will the requirements for maternal immunizations be the same as for other vaccines?
- **Challenges assessing AEs post-licensure:**
  - Healthcare settings for administration of vaccine to pregnant woman and follow-up of infant differ, making it difficult to link vaccination of mother and AEs/outcomes in infants.
- **Creation of a robust post-marketing surveillance system will be critical.**
  - Significant improvements in pregnancy registries are needed.

# Policy Challenges

# Clarification of the Liability Environment

- VICP protects patients, providers and manufacturers.
- The NVAC Maternal Immunization WG and the ACCV have developed a strong set of recommendations with broad stakeholder support.
- NVAC MI WG and ACCV enthusiastically support the extension of liability protection for maternal immunization.
- **Actions could be undertaken by NVAC and the stakeholder community to encourage the implementation of these recommendations by the Secretary of HHS.**

# ACIP Recommendation Process

- An ACIP recommendation is critical as it defines the environment for a vaccine by facilitating both uptake and insurance coverage.
- There is much uncertainty related to the recommendation process for novel maternal immunizations to protect pregnant women, infants, or both.
  - Accurate burden of disease data will be critical.
  - The recommendation process must acknowledge the changing environment for acceptable measures of clinical efficacy, especially as these were developed to accelerate R&D for novel products for an unmet medical need.
- Industry needs clarity regarding the **standards of acceptable evidence for efficacy and effectiveness.**
- *Joint discussions between FDA, CDC and sponsor may help facilitate this.*

# Summary of Key Points

- **Companies are committed to public health and are investing in maternal immunizations.**
  - The efforts of federal agencies and stakeholders to establish a maternal immunization platform help make these investments feasible.
- To date, only flu and Tdap vaccines have recommendations for use in pregnant women, and industry considers the lack of a specific indication in the label as a limit to their ability to discuss the recommendation.
- Companies are the best place to clinically develop maternal immunizations due to scientific and regulatory expertise, capacity and resources.
- **Investments in maternal immunization data for existing and new vaccines will continue to increase as stakeholders work together to resolve clinical development and policy challenges.**
  - Strong communication and guidance on key clinical issues, such as appropriate endpoints and trial design, from FDA and CDC;
  - Clarity on the issues affecting liability.



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