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.
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?
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.
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.
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.
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.
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.
Biotechnology Industry Organization