Advancing Regulatory Science

FDA describes mechanism potentially responsible for respiratory side effect associated with pig influenza vaccine

The results of a study in pigs led by scientists at FDA suggest that researchers attempting to develop a "universal" influenza vaccine targeting a specific part of influenza viruses called the HA stem should consider the possibility that some antibodies triggered by such a vaccine might enhance influenza disease rather than prevent it.

"Vaccine-induced anti-HA2 antibodies promote virus fusion and enhance influenza virus respiratory disease"

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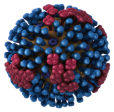
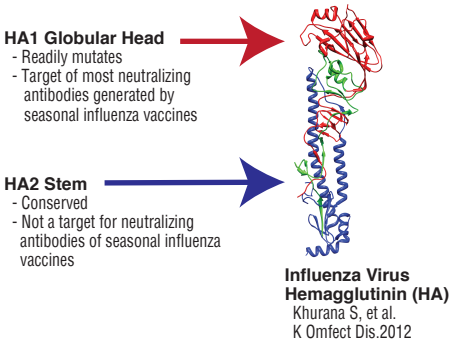


Influenza A (H1N1 2009 virus
Dan Higgins, CDC

Development of Safe and Effective Universal Influenza Vaccines

- Vaccines that prevent influenza trigger production of antibodies against a protein called hemagglutinin (HA). These antibodies inhibit virus infection by preventing HA from binding to cells in the body. HA is therefore the key component of most influenza vaccines.
- The globular head of HA (HA1), which enables the influenza virus to attach to cells, mutates readily. This alters the protein so it can evade attack by antibodies. Therefore, new seasonal vaccines are required each year.
- The current process of making, distributing and administering millions of doses new seasonal influenza vaccines each year could become obsolete if researchers could develop a universal influenza vaccine that provides long-term protection from any influenza virus strain that may circulate.
- The antibodies triggered by a universal vaccine are called cross-reacting because they attack targets on other influenza viruses that are conserved; that is, they attack those targets that do not mutate readily and therefore are very similar or identical from one influenza virus to another.
- The goal of some universal vaccines in development is to elicit antibodies that target exclusively the stem region of HA (HA2), which contains the "fusion peptide" that enables the cell-bound virus to enter the cell and infect it. The prediction is that antibodies that target the stem of HA will block virus fusion, thereby slowing or blocking the virus from infecting the cell.



Vaccine-Associated Enhanced Respiratory Disease

- A previous USDA study found that pigs vaccinated with whole inactivated vaccine containing a human-like H1N2 and subsequently challenged with pandemic 2009 H1N1 (pH1N1) virus had enhanced pneumonia and respiratory disease compared to non-vaccinated animals exposed to pH1N1. (Vincent, AL, et al. *Vet Microb* 126:310-323 [2008])

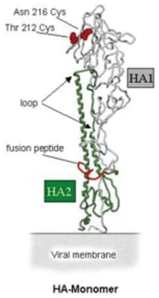
FDA/USDA Study Describes Novel Mechanism Potentially Responsible for Enhanced Respiratory Disease Associated with a Pig Influenza Vaccine

Mismatched Vaccine and Antibodies

- Study was based on a mismatched pig influenza vaccine; i.e., a vaccine based on one influenza virus that is used to protect against a different influenza virus. Such a vaccine elicits cross-reacting antibodies.
- The pig vaccine was based on inactivated (killed) H1N2 influenza virus, which triggered both anti-HA1 and anti-HA2 antibodies in pigs.

Results of FDA Study

- The vaccine used in the study is specifically for pigs and is not the same type of influenza vaccine that millions of people receive every year.
- Anti-HA1 antibodies elicited by H1N2 vaccine blocked HA1 domain following exposure to the H1N2 virus vaccine virus, preventing H1N2 viruses from attaching to cells.
- Both anti-HA1 and anti-HA2 antibodies elicited by the H1N2 vaccine failed to protect against a different (mismatched) virus, pH1N1 (the virus that caused the 2009 influenza pandemic); moreover, all infected animals showed enhanced pneumonia and lung damage.
  - Anti-HA1 antibody elicited by H1N2 vaccine did not recognize HA1 on pH1N1 virus; therefore, the antibody failed to block the pH1N1 virus from attaching to cells in the lungs of vaccinated pigs.
  - Anti-HA2 antibodies triggered by the H1N2 vaccine did recognize the conserved HA2 protein (Stem region) on pH1N1. However, the binding of these antibodies to HA2, which contains the **fusion peptide**, enabled the pH1N1 viruses to fuse more effectively with lung epithelial cells. This caused enhanced disease in animals that had received the H1N2 vaccine and were subsequently exposed to the pH1N1 virus.



This study describes a specific immunological mechanism leading to the production of antibodies that may affect the safety of a particular type of universal vaccine designed to elicit stem-targeting antibodies (but no receptor-blocking antibodies).
The findings contribute important insights to the ongoing research efforts toward developing safe and effective universal influenza vaccines.