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Age and Gender Difference in the Immune System Response to the 2009 H1N1 Pandemic Influenza Virus

Evidence for a qualitatively superior antibody response in the elderly following H1N1 pdm09 vaccination might help to explain why there was lower morbidity and mortality in older populations during the 2009 H1N1 influenza pandemic.

Journal of Infectious Diseases

"Immune response following H1N1pdm09 vaccination: difference in antibody repertoire and avidity in young and elderly populations stratified by age and gender"

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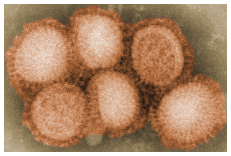


Morbidity and mortality from the 2009 H1N1 influenza pandemic virus lowest among adults over 65 years of age

- Adults over 65 years suffered lower rates of morbidity and mortality from the 2009 H1N1 influenza virus pandemic than did children and young adults—a reversal of the pattern usually seen during influenza epidemics.
- This unusual pattern of morbidity and mortality was reminiscent of the 1918 Spanish influenza, which also disproportionately affected children and young adults.
- Various explanations offered to explain the lower attack rate and lower frequency of severe disease in the elderly were not supported by conclusive data.

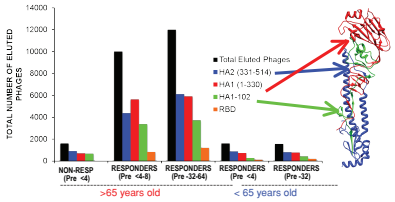
Discovering why the elderly have a superior antibody response to the H1N1pdm09 vaccine

Previously, a large phase 2 clinical study found that a single dose (7.5, 15, or 30 ug) of a monovalent unadjuvanted H1N1pdm09 split virus vaccine induced protective antibody levels in adults of all ages, including elderly adults. In the current study, CBER scientists evaluated sera from 168 individuals using powerful techniques that assessed both the targets of the antibodies and their ability to bind to those targets.

- Genome-fragment-phage display libraries (GFPDL): Genetically engineered phages that displayed a wide variety of peptides of H1N1 probed the complete antibody epitope repertoires of sera from individuals who participated in a Phase 2 clinical trial that studied the effectiveness of the H1N1pdm09 vaccine.
- Surface Plasmon Resonance (SPR): This optical sensor-based technique was used for determining strength of interactions between biological molecules in real time, measured how long antibodies remained bound to antigenic domains of recombinantly produced influenza HA epitopes identified by GFPDL.

Identifying antibody targets with genome-fragment-phage-display libraries

Graph below shows differing responses of non-responders and responders to the H1N1 pdm09 vaccine as measured by the number of different phage-displayed epitopes bound to various post-vaccination serum antibodies. Figures in parentheses refer to the pre-vaccination titers of antibodies against these epitopes before vaccination.



- H1N1pdm09 vaccination induced 10-fold higher antibody levels in elderly compared to younger adults.
- Antibodies from the elderly group (> 65 years) generated by the vaccination selected phages displaying a greater variety of viral epitopes than did antibodies from the younger group (< 65 years).
- Elderly adults also produced antibodies against more epitopes on the receptor binding domain (RBD) of the HA1 domain, the key site for attachment of the virus to the cells it infects.

Assessing anti- HA antibody binding avidity using Surface Plasmon Resonance

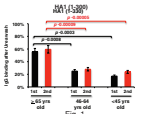


Fig. 1

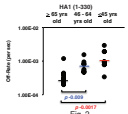


Fig. 2

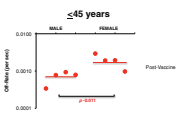


Fig. 3

- Post-vaccination antibodies from elderly demonstrated higher anti-HA1 avidity than from younger subjects as demonstrated by higher resistance to 7M urea treatment in ELISA (Fig.1).
- Elderly responders showed slower antibody dissociation rates to HA1 than middle age (46-64 yrs) and young adults (<45 yrs) following H1N1pdm09 vaccination (Fig.2).
- Post-vaccination antibody avidity to the HA1 globular domain was significantly greater in male adults than in female adults (Fig 3).

CBER scientists in the Office of Vaccines Research and Review showed that the epitope repertoire, affinity, and avidity of HA-1-bound antibodies following H1N1 pdm09 vaccination were superior in the elderly compared with younger adults.

These finding support the conclusion that >65 year old individuals have long-term memory B cells that recognize H1N1pdm09 presumably due to previous exposure to similar viruses. These findings, in addition to the use of newly developed assays used in this study, are likely to improve our understanding of the clinical outcomes of influenza vaccination in different populations, especially as new types of vaccines and novel adjuvants are developed and evaluated.