Author's response to reviews

Title: Differential immune responses in individuals after the 2009 pandemic influenza infection and after vaccination with the pandemic influenza vaccine: A prospective study in Sweden

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Dear Editors

please find enclosed our manuscript

Differential immune responses in individuals with PCR+ H1N1 as compared to vaccination with the pandemic flu vaccine in a prospective study in Sweden

for consideration for publication in BMC Medicine.

A number of studies have now been published in the aftermath of the H1N1 epidemic. More recent reports (list below, e.g. Wilkinson et al., Nature Medicine, 2012. Jan 29, epublished ahead of print. Pre-existing influenza-specific CD4+ T-cells correlate with disease protection against influenza challenge in humans) pointed out that preexisting CD4(+), but not CD8(+), T cells responding to influenza internal proteins were associated with lower virus shedding and less severe illness.

We represent here the data from a comprehensive prospective study (n= 2000 participants) from Sweden which has unique points:

Access to time’ point 0 samples’, i.e. before vaccination and before H1N1 infection .

It allowed for the first time a comprehensive and robust analysis of differences in individuals who received the H1N1 vaccine and individuals who were infected with H1N1 (defined by PCR). This point is particularly interesting since data from the MPA in Sweden and Finland underline that H1N1 vaccination (the adiuvanted vaccine from GSK) was apparently associated with an increased risk of narcolepsy in these countries and the analysis of these patients is currently underway.

We could identify the immune response in individuals who reported zero symptoms during the Flu period, yet these individuals showed an immune recognition pattern indicative of a silent infection - characterized by a specific antibody and cellular recognition pattern.
Three points are novel and highlighted:

1. Individuals with H1N1 show a different immune response as vaccinated individuals, concerning the cellular target pattern recognition and the \textit{duration} of the immune response.
2. Vaccinated individuals show a strong M1 response – this is not contained officially in the vaccine and we excluded (by PCR and by antibody titers) the possibility that these individuals were exposed to H1N1. Vaccines (according to a technical report and after discussion with GSK) contains also M1 – and this appears to be a crucial factor for immune protection.
3. Individuals may have been exposed to H1N1 (based on increased cellular and humoral reactivity) without experiencing symptoms. This pattern will lead the way to new Flu vaccines.

\textbf{Related Literature:}


K.L Laurie et al., \textit{Infect Dis.} 2010 Oct 1;202(7):1011-20. \textit{Multiple infections with seasonal influenza A virus induce cross-protective immunity against A(H1N1) pandemic influenza virus in a ferret model.}


S. Khurana et al., \textit{J Infect Dis.} 2012 Feb;205(4):610-20. Epub 2011 Dec 29. \textit{Immune Response Following H1N1pdm09 Vaccination: Differences in Antibody Repertoire and Avidity in Young Adults and Elderly Populations Stratified by Age and Gender.}

We hope that the report is of interest to the readers of BMC Medicine

\textit{For the authors}

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