

PRE-EXISTING IMMUNITY: A FITNESS INDEX FOR INFLUENZA VACCINATION

To the Editor,

Unprecedented mutability and unpredictability render the influenza virus one of the most serious threats to human health and pose an unusual challenge to basic virology, immunology and vaccinology [1]. As a mirror image of the situation, there hardly exists another field in vaccinology with so many variable, inconsistent and conflicting reports. In spite of low-to-moderate efficiency of flu vaccines, vaccination remains both a key tool in combating the virus today and our major hope to control it in the future. Current practice implies a 'universal' vaccination in the United States and selective vaccination of high risk groups in other countries. We argue that this 'universal' approach, which eliminates the difference in pre-vaccination immunity status of vaccinees, is not constructive on a large scale and in the long run.

There are two players in vaccination, a vaccine and a vaccinee/recipient, and each one can be suitable or unsuitable for vaccination. Paradoxically, vaccination is aimed to protect vaccinees, yet their fitness for vaccination is largely ignored. It should be emphasized that pre-vaccination/pre-existing immunity (PEI) against influenza virus – in particular pre-existing antibodies (PEA) – is widely recognized de facto as influencing immune response to vaccination. However, PEI is considered a confounding factor that interferes with evaluation of vaccination efficiency and thus should be corrected for after immunization. In our vision, PEI is a natural highly variable individual feature of vaccinees that must be taken into account and underlies differentiation and stratification of vaccinees prior to vaccination.

The individual diversity of PEI and ensuing high variability of post-vaccination immune responses is a fundamental feature of an adaptive immune system, and each person has their own adaptive immune repertoire. None of the risk-stratified groups, not to mention the entire population, is homogeneous with regard to PEI.

Our results strongly confirm this point: only stratification by PEA and dividing the original population into homogeneous low and high PEA carriers allowed meaningful reproducible results upon active immunization. We observed a negative correlation between the levels of PEA and post-vaccination antibodies. Immunization of high PEA carriers did not produce adaptive antibodies but could be dangerous by consuming the relevant PEA at the first stage of vaccination without mounting the adaptive immune response [2].

With regard to suitability, there are four possible interactions between a vaccine and a recipient, and only one would be really beneficial – a suitable vaccine and a suitable recipient. The other three options will probably be of no use at best. By ignoring diversity, considering individuals immunologically homogeneous and advising universal vaccination, we are making a serious mistake and expose people who do not need vaccination to unnecessary risk. Recent deaths of elderly people in Italy this last winter and earlier in other countries and the discovery of autoimmune events shortly after the flu shot [3,4] might sound the warning bell.

Our approach to legitimize PEI as a stratification index prior to vaccination does not mean of course that we advocate a personal vaccine for everyone, which is utopia. However, refinement of this novel index, creation of national infrastructures with regularly updated banks of relevant data (personal sera and medical history), and development of new technologies enabling fast computerized individual evaluations is within reach.

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The authors dedicate this letter to the memory of all those whose death was caused by vaccination.

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INTERFERON-GAMMA-RELEASE ASSAY PREVENTS UNNECESSARY TUBERCULOSIS THERAPY

To the Editor,

In their recent article, Schichter-Konfino et al. suggest that a negative interferon-gamma release assay (IGRA) obviates the need for latent tuberculosis treatment among patients with a positive tuberculin skin test (TST) [1]. However, there are limitations in their study that render its results inconclusive.

First, the study population was not a random sample of a population undergoing the Mantoux TST. The subjects had in fact their own reasons for undergoing the IGRA test following a positive TST and were willing to pay for its cost. Therefore, there is a high probability of a selection bias in the study. Second, the authors did not provide details regarding the Bacillus Calmette-Guerin (BCG) vaccination status of the subjects. This is important since a positive TST (due to previous vaccination with BCG) with a negative IGRA is commonly found under these circumstances [2]. Furthermore, the immigration status (and country of immigration) is not presented. It is this information that determines the pre-test probability of TB infection and is therefore a vital component of any analysis of TST screening results. This omission further weakens the validity of the authors' conclusions.

In addition, it was recently shown that in health care workers undergoing serial tuberculosis (TB) screening in a low TB incidence country there was a six to nine times more frequent false IGRA test conversion rate than TST [3]. Another limitation of this study is the small number of participants, 99, with a negative IGRA and a positive TST. A larger, random sample population with adequate background information and a longer follow-up period

are needed to resolve these important issues and one should view the conclusions of the authors with caution.

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To the Editor,

In reply, indeed, our main point in this study was to focus on the higher specificity of IGRA.

As mentioned in the Patients and Methods section, all individuals referred for IGRA testing were: (i) medical staff in whom TST was found positive, (ii) candidates for anti-TNF therapy in whom TST was positive and were advised to take anti-TB therapy, and (iii) individuals who were in contact with TB patients and advised to undergo IGRA as a primary test.

Although not fully randomized, this is a representative population of real-life individuals who presented to our facility due to TST positivity; therefore, any bias here is very low. The status of BCG vaccination in our tested population is indeed not detailed. These individuals have a higher incidence of TST and a larger size of skin reaction. Our results did not show any correlation between

IGRA positivity and TST size. In addition, one should remember that almost all previous studies in this respect refer to the high specificity of IGRA in BCG-vaccinated individuals. Therefore, our IGRA results should be considered highly specific and with no relation to the number of BCG-vaccinated individuals. The countries of immigration of our studied population were mainly Russia (90%) and Ethiopia (both highly endemic for TB). While this could be added to our Patients and Methods, this information is relevant to the issue of TST positivity but not to IGRA specificity which was the main issue in our study. Finally, the long-term follow-up of our IGRA-negative individuals strengthens the high specificity of this test. We of course agree that further studies should confirm our results.

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