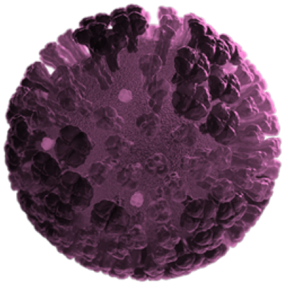
Global Influenza Initiative



InFluNews

The monthly newsletter from the Global Influenza Initiative (GII)

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Welcome to the November issue of InFluNews!

*In the previous issue of InFluNews we presented highlights from the European Society of Cardiology congress, focusing on four presentations which described the impact of influenza on cardiovascular disease and the benefits of influenza vaccination. If you have missed any of the past issues of InFluNews or would like to find out more about the GII, please visit the **GII LinkedIn page**.*

Personalised vaccinology: Implications for future influenza vaccines

The concept that immunogenetics and immunogenomics can be applied to the study of vaccine-induced immune responses was described by Poland et al. in 2008. Poland et al. described how variations in immune response genes lead to differences in humoral, cell-mediated and innate immune responses to vaccines at both the individual and population levels.[1,2]

This information can then inform and allow the development of personalised vaccines. The intention is not to develop a unique vaccine for each individual but to develop vaccines designed to optimise the outcome of vaccination in different populations, for example, in people of different genders, race/ethnicity or ages.[1,2]

The availability of 'Big Data' is enabling a move away from the classical 'one size and dose fits all' approach to vaccinology to a more tailored and personalised approach to vaccine design and administration.[3,4]

This month's guest editor, Raina MacIntyre provides expert commentary.

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH:

Key factors that lead to variation in response to vaccination

Gender-based differences

Females tend to mount stronger immune responses to infectious diseases than males. Similarly, immune responses to inactivated influenza vaccines are greater in females than in males. There is some evidence for greater vaccine effectiveness in females than males, but insufficient sex- and age-disaggregated data to support a definitive conclusion.[5]

Gender-specific effects of aging have also been observed. For example, pre-vaccination titres to the high-dose inactivated influenza vaccine decrease with age in males, but not in females, and antibody titres to the 2009 pandemic H1N1 vaccine have been shown to decrease with age in females, but not in males.[5]

Immunosenescence is: *'an age-related dysregulation of the immune system due to age-associated changes in innate and adaptive immune system components, which leads to impaired immunity and protection following immunization or infection.'*

Poland et al. (2018)[6]

Age-based differences

Studies have shown how specific parts of the innate immune system are affected by immunosenescence in the elderly. Immune dysfunction is observed through altered cytokine secretion, decreased NK cell activity, reduced TLR expression, and a chronic inflammatory state that has been termed "inflamm-aging". However, the systems-level mechanisms for the impaired immune responses of older people to influenza and other viral vaccines are not well defined.[6]

Vaccines have been developed with the aim of overcoming age-related declines in immunity. For example, the adjuvanted zoster subunit vaccine contains a novel adjuvant ($AS01_B$) which stimulates the innate immune system and leads to an improved T-helper cell response in older adults.[6]

The adjuvant GLA-SE, a TLR-4 agonist, has also been shown to enhance T-helper cell responses (Th1 subtype) to influenza vaccine in older adults, adding further evidence that targeting innate receptor agonists that enhance innate immune responses against influenza is an effective means of overcoming the age-related decline in vaccine-specific immunity.[6]

Race/ethnicity

Studies have shown that ethnicity influences the immune response to several different vaccines. Examples include rubella, measles, pertussis and influenza vaccines.[7] A 5-year study analysed antibody and B-cell responses to the influenza A virus components of the inactivated influenza vaccine, trivalent or quadrivalent vaccines in younger and older Caucasian and African American adults. The study showed that younger African Americans mounted higher antibody responses to the H1N1 component of the trivalent or quadrivalent vaccines compared to younger Caucasians. African Americans also had higher levels of circulating B-cell subsets compared to Caucasians and showed differences in B-cell phenotypes. This study suggested that genetic and/or lifestyle factors and vaccination history all contribute to the differences in the immune responses observed between different races.[7]

HLA system polymorphism

The human leukocyte antigen (HLA) system plays a key role in stimulating T-cell responses to pathogens or vaccine antigens, and a subset of T-cells, T-helper cells, are also required to support antibody production. HLA genes therefore play a significant role in genetic susceptibility to infectious diseases and in causing variation in vaccine-induced immune responses.[2]

As an example, several gene association studies involving measles-mumps-rubella (MMR) vaccines conducted by Poland and colleagues have demonstrated the link between specific HLA haplotypes and variations in measles- and mumps-specific immune responses.[2,6]

Immune response gene polymorphism

Polymorphism in immune response genes can also lead to variations in vaccine-induced immune responses. For example, Toll-like receptor (TLR) genes form an important link between innate and adaptive immunity. Poland et al. have demonstrated links between measles vaccine-induced humoral responses and polymorphisms in the TLR2 and TLR4 genes; rubella-specific granulocyte-macrophage colony-stimulating factor (GM-CSF) production and polymorphism of the TLR3 gene; a decrease in mumps vaccine-induced antibody titres and a TLR4 polymorphism, and an increase in T-cell responses and a TLR5 polymorphism.[6]

Previous vaccination or infection

The immune response to influenza vaccination can be modified by past influenza virus infection and past vaccination. It is well recognised that the antigenic properties of the influenza virus that a child is first infected with can shape their response to exposures later in life; for example, an age cohort effect, based on year of birth, was seen in vaccine-induced immunity to 2009 pandemic influenza A(H1N1) viruses.[8] A recent study showed that those with and without prior season vaccination had increased benefits from vaccination[9], although other studies, especially those involving A(H3N2) viruses have suggested that repeated vaccination increases influenza risk.[8] Given these somewhat conflicting data, it is clear that vaccine effectiveness studies considering prior vaccination across multiple seasons by virus type and subtype are needed,[9] and these data will be required for the optimal design of personalised influenza vaccines.

Predisposition for adverse events

The COVID-19 pandemic has put vaccines in the spotlight, raising public awareness of the importance of vaccination, drawing attention to vaccine effectiveness and safety, but also highlighting the fact that some people may be unresponsive to vaccination or suffer side effects.[10]
A predisposition for adverse events is being studied by identifying predictors or immune signatures of adverse immune outcomes, i.e. those that lead to harm rather than benefit. This would also contribute to a move away from a 'one size and dose fits all' approach to one where we are able to better understand how different factors affect the propensity to experience adverse events and adjust our approach to vaccination accordingly.[6]

Research has shown associations between specific genes or SNPs and adverse immune outcomes following smallpox vaccination, illustrating the potential application of this approach to other vaccines commonly used in the general population.[6]

Some key challenges to realising personalised vaccinology[2,4,6,11]

Thinking and perception

- Accepting a new paradigm of thinking[4]
- Moving away from a population-based, mass vaccination approach to an individualised approach[2]
- Countering the perception that personalised medicine is expensive[11]

Data and technologies

- Need for larger genotype:phenotype data sets[6]
- Need to describe levels of vaccine-induced protection in different population groups
- Need for studies to confirm that modification of vaccines improves protection in different population groups
- Need for improved technologies[6]

Progress in personalised medicine

'The purpose of personalised medicine is: 'to combine the ancient philosophy of treating patients individually with modern tools made available by the advent of big data, in order to improve the efficacy, safety and effectiveness of the therapeutic approach'. Teodori et al (2022)[12]

COVID-19

The COVID-19 pandemic and the subsequent rapid advancement of COVID-19 vaccines has also accelerated the discussion around the application of OMICs technologies (genomics, proteomics, lipidomics etc.) to the study of COVID-19 and development of effective vaccines and provided an opportunity to advance personalised health in this field.[10,12,13]

Teodori et al. (2022)[12] provide an overview of the progress achieved in personalised medicine approaches against SARS-CoV-2. A key achievement in this area is in the field of SARS-CoV-2 genetics. Monitoring of SARS-CoV-2 genetic variations alerts us when new variants emerge, including variants of interest, and variants of concern. This has allowed vaccine manufacturers to modify the vaccine strain to match the circulating virus strain more closely.

Individual genetic make-up also affects susceptibility and response to SARS-CoV-2 infection. Several initiatives have been established during the pandemic to better understand the impact of host genetics.[12] These include, for example, the Host Genetics Initiative, a global, open-source initiative established to share COVID-19 data, methods and resources.[12,14]

High-throughput 'multi-omics' approaches are allowing host responses to SARS-CoV-2 to be characterised across different patient phenotypes (e.g. asymptomatic, severe and critical patients). This allows individual host 'signatures' to be described including immune, proteome, lipidome and epigenetic signatures.[12]

The severity and particular challenges of the COVID-19 pandemic have led to rapid advancements in personalised health and illustrated the potential of a personalised medicine approach in addressing other infectious diseases, including influenza.

Influenza and pneumococcal vaccines

Influenza vaccines have already achieved a degree of personalisation, although this is largely based on vaccine effectiveness rather than on immunogenetic data. For example, in the US, multiple different influenza vaccines are available, allowing vaccines to be selected according to age group, and other factors (e.g. recombinant vaccines for those who have egg allergies; needle-free vaccines for those who are needle-phobic).[5] Despite the availability of so many different vaccines, the CDC currently only makes preferential vaccine recommendations for those over 65 years of age, but not for those under 65 years.[15]

Four different pneumococcal vaccines are also FDA-approved and recommended by the CDC. The vaccines are licensed for different age groups and the CDC's recommendations vary according to age, which pneumococcal vaccines were previously received, and risk factors. (For a full description refer to: Ask the Experts: Pneumococcal Vaccines (immunize.org)).[16]

Expectations for the future of personalised vaccines

Dr Gregory Poland has stated that we should abandon a "one size and dose fits all vaccine approach" and instead use an approach where we predict whether to give a vaccine based on likelihood of response.[4] In the future we should also be able to predict the likelihood of a significant adverse event to a vaccine and the number of doses likely to be needed to induce a response to a vaccine in a given population.[4]

Poland predicted a move towards a 'Vaccinology 3.0' approach which integrates immunogenetics and systems biology into vaccine design and development, a greater use of advanced adjuvants and antigen packaging systems, and the development of new vaccines for specific population subgroups.[4]

COVID-19 highlighted the need for a more personalised approach to medicine and pushed us closer to achieving that in several areas. Some vaccines, such as influenza and pneumococcal vaccines have already achieved a degree of personalisation, but as with most vaccines, still have a long way to go to fully integrate a personalised approach into vaccine design and development, based on the key factors we have described above.

Guest editor Raina MacIntyre comments:

The promise of personalised vaccinology is already being realised, as outlined by Dr Gregory Poland. Examples include the use of high-dose and adjuvanted influenza vaccines for older adults, which provide increased protection compared to standard-dose vaccines. Immunosenescence, a predictable decline in the immune system from the age of 50 years onwards, results in lower immunogenicity of all vaccines in older adults. In the past, vaccinology in older people has not been a priority, because of a perception that there are low returns in elderly vaccination – yet breakthroughs in influenza vaccines and also in herpes zoster vaccines that result in high efficacy, have started to shift this perception. Taking that a step further, it is conceivable we can personalise vaccines for individuals based not only on their age, but on gender, HLA type and immune response gene polymorphisms. COVID-19 may help advance this field, given it is the largest whole-population vaccination programme since smallpox vaccination.

GII Summary Statement

Vaccination became the focal point of global conversations amongst researchers, healthcare professionals and the general public during the COVID-19 pandemic. Whilst vaccine effectiveness, safety, and variability of response were hot topics for all audiences, the necessity for rapid vaccine production brought the application of OMICs technology to the forefront. This significantly advanced the personalised vaccinology discussion.

Significant progress is being made in the field of personalised vaccinology, particularly in relation to immunogenetics, immunogenomics, and vaccine-induced immune responses at both the individual and population level. However, with certain challenges and concerns remaining, there needs to be an improvement in technologies, larger studies, and a paradigm shift from mass population to an individualised vaccination approach.

Moving into the future, the ‘one size fits all’ approach is becoming redundant in the field of vaccinology. The integration of advances in immunogenetics and immunogenomics into vaccine design and development promise to build on the personalised vaccine journey, to ultimately meet the needs of specific population subgroups.

About the GII

The GII is a global expert scientific forum that includes international scientists, researchers and clinicians with expertise in epidemiology, virology, infectious diseases, immunology, health economics, public health, primary care and geriatrics. The GII receives financial support from Sanofi which covers the involvement of Ogilvy Health, a medical communications agency which acts as the secretariat for the GII as well as coordinating logistics for the annual meeting, managing other GII projects and offering strategic counsel.

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