Vaccination Challenges and Their Solutions

Adverse effects and reactions to vaccines have been drawing public attention and threatening public health success in vaccination programmes despite the tremendous decreases in infectious diseases worldwide.[1] The technology advancement in genome scanning, epigenetics, transcriptomics and proteomics enable novel approaches to the understanding of the adverse effects and reactions to vaccination in children. Understanding the association and mechanism of factors related to adverse vaccination reactions will assist in minimising adverse events and provide more of a personalized approach to vaccination.

1. Genetic challenges to Vaccination

Vaccination relies on immune responses to generate infection protection; and these immune responses are under the control of genes with individual polymorphisms. Naturally individuals with various genetic backgrounds will react to vaccination differently. For example, after the live rubella vaccination, several immune function related gene SNPs (Single Nucleotide Polymorphisms), such as PVR, PVRL2, CD209/DCSIGN, RARB, MOG, and IL6 involved in humoral immune responses and neutralizing antibody production to cause individual different humoral immune reactions;[2] and BTN3A3/BTN2A1, IL10RB/IFNAR1, PVR, and ADAR involve in cellular immune response to cause individual different cellular immune reactions.[3] A further study confirms that the human leukocyte antigen (HLA) DPB1 gene polymorphism is significantly associated with humoral immune responses to rubella vaccination, resulting in various neutralising antibody levels.[4]

Serogroup B and C meningococcal conjugate vaccination protected populations worldwide from the invasive disease. A study found that gene SNPs of TLR3 and CD44 are associated with IgG concentration and anti-bactericidal antibody levels after serogroup C meningococcal conjugate vaccination in infants.[5] Interestingly,

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a vitamin D receptor gene SNP is shown to be significantly associated with immune responses to hepatitis B vaccination (HBV) in renal replacement patients.[6] Its AA homozygotes have higher risk to be non-responders than its GG homozygotes. This is critical because immune responses against HBV is crucial for these patients.

A review shows that more than ten different gene SNPs are associated with measles vaccination.[7] These gene SNPs are CD46, SLAM, IL12B, DDX58, IFNA1, IL2RB, IL4, IL6, IL8RA, TLR2, TLR4, TLR5, TLR7, VISA, and TRIM5; and they are either HLA gene haplotypes, or gene polymorphism directly related to the immune responses. These gene SNPs, function individually or in combination and result in individual variation in measles vaccine induced antibodies, and play roles in vaccination success or failure.

The above information indicates the inter-individual variation observed in immune responses from vaccination of different vaccines. Better understanding of genetic factors and their association to individual vaccination related immune responses assists in the determination of quality and quantity of vaccines, route of immunisation, number of doses, and vaccination schedules.

2. Autoimmune disease challenges to Vaccination

Vaccination has been linked to autoimmune responses or diseases.[8] It is found that four groups of preliminary conditions may be susceptible to autoimmune / inflammatory syndrome induced by adjuvants (ASIA). These preliminary conditions are:

- Prior post-vaccination autoimmune phenomena;
- History of autoimmunity;
- History of allergy;
- Prone to develop autoimmunity such as carrying certain genetic profiles, asymptomatically carrying autoantibodies; and having a family history of autoimmune diseases.

Most autoimmune diseases and their development bear a strong heritable

32(27): 3424-30. PubMed PMID: 24768503

[6] Grzegorzewska AE, Jodłowska E, Mostowska A, Sowińska A, Jagodziński PP. Single nucleotide polymorphisms of vitamin D binding protein, vitamin D receptor and retinoid X receptor alpha genes and response to hepatitis B vaccination in renal replacement therapy patients. Expert Rev Vaccines. 2014 Nov; 13(11): 1395-403. PubMed PMID: 25245883

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[8] Soriano A, Nesher G, Shoenfeld Y. Predicting post-vaccination autoimmunity: who might be at risk? Pharmacol Res. 2015 Feb; 92: 18-22. Review. PubMed PMID: 25277820

background.[9] The genetic contribution to autoimmunity is complex ranging from strong autoimmune susceptible alleles to the interaction between multiple weak autoimmune loci. Genetic background causes different reactions and pathogenic consequences in individuals to the same vaccine or different combination of vaccines. Fortunately, genetic susceptibility related to different autoimmune diseases are found and available to enable gene diagnostic screening to avoid ASIA.

Multiple HLA gene regions, for example, are found to be strongly associated with autoimmune diseases.[10] In these HLA gene regions, DR2 is found to increase the risk for Goodpasture's syndrome and multiple sclerosis; DR3 to increases the risk for SLE, celiac disease, Graves' disease and type 1 diabetes; DR4 to increase the risk for pemphigus, rheumatoid arthritis and type1 diabetes; and DR5 to increase the risk for pernicious anaemia and Hashimoto's thyroiditis. As a consequence, an appropriate pre-diagnosis of autoimmune conditions will help to design appropriate vaccine and set various vaccination schedules for individual children with autoimmune susceptibility.

3. Autism and vaccination challenges

Autism has been linked to vaccination for more than a decade. The most recent and convincing study is an evaluation of overall vaccination on autism in older children (studies on younger children may not be sufficient due to incomplete vaccination schedules), of all U. S. states from 2001 to 2007.[11] It found that autism or speech impairment increased 1% in all vaccinated children. The evaluation suggests a possible link between a battery of vaccination and autism development. Even though mercury has been removed from multiple vaccines, the evaluation assumes that other non-active components such as aluminum and thimerosal, are either neurotoxin or immunosuppressant damaging the brain of the vaccinated children and resulting in their susceptibility to autism.

It is unclear if it is the individual vaccine or a combination of vaccines that cause autism. What is clearer currently is that genetic factors have effect on autism susceptibility. Several genes, such as GSTM1, GSTP1, PON1, SLC11A3, δ-aminolevulinic acid dehydratase, and metal regulatory transcription factor 1, increase the susceptibility of autism. Children carrying these genes are more susceptible to vaccination induced autism, and thus they need individualized

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[10] Gough SC, Simmonds MJ. The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action. Curr Genomics. 2007 Nov; 8(7): 453-65. PubMed PMID: 19412418

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vaccination.

Environmental toxicants may make those children carrying susceptible genes more sensitive to vaccination.[5] A systemic review of nine scientific databases suggests that these toxicants are air pollutants, pesticides, phthalates, polychlorinated biphenyls, solvents, toxic waste sites and heavy metals, in which the strongest evidence is found for air pollutants and pesticides.[12] The review supports the notion that shared environmental and genetic factors could result in the development of autism. These children may have lower detoxification, higher oxidative stress, altered hormone levels, and altered neuronal development; and thus they need personalized vaccination.

A debate of vaccination and autism is ongoing concerning the qualities and reliabilities of related studies. For example, a letter from Australian scientists questions the research qualities of a meta-analysis of ten vaccination and autism studies which denies the relationship between vaccination and autism.[13] The letter claims that the meta-analysis is not scientific because it fails to compare the autism incidence between vaccinated and unvaccinated populations; and thus it is not convincing to draw the conclusion based on no difference of autism rates between different vaccinated groups alone. Another report shows that, thus far, there is no strong evidence showing the impact of MMR vaccination and autism.[14] As a consequence, the Lancet retracted a paper completely about the positive impact of MMR vaccination on autism to avoid misleading the scientific society. This indicates that, even though regression studies confirm the relation between vaccination and autism, it remains unsure if autism is a consequence of the combination of vaccines or individual vaccines.

4. Other challenges

Immune responses induced by vaccination are necessary for the infection protection effects. But if these immune responses are over-reactive, it is called allergy and it will bring in variation and challenges from vaccination.[15] Vaccination related allergy is mostly induced by the additional components in vaccines, such as additives, adjuvants, preservatives, and traces of other substances. The additional or non-reactive components are added either to enhance the immune

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[15] Franceschini F, Bottau P, Caimmi S, Crisafulli G, Lucia L, Peroni D, Saretta F, Vernich M, Povesi Dascola C, Caffarelli C. Vaccination in children with allergy to non active vaccine components. Clin Transl Med. 2015 Feb 14; 4: 3. PubMed PMID: 25852819

response or to prolong the life-time of the vaccines. But they have a tendency to induce allergy or hypersensitivity reactions; and they should not be neglected, particularly when a high number of doses are administrated. Individual allergological evaluation can be used to seek suitable vaccines, routes, and schedules with material and support for treating anaphylaxis.

Table 1. Vaccination Checklist for Currently Found Genetic Polymorphisms (2017)

Genes & Genetic polymorphisms	Related vaccines	Related immune reaction	Publications
PVR	Rubella	Antibody variation	2. Haralambieva et al., 2014
PVRL2	Rubella	Antibody variation	2. Haralambieva et al., 2014
CD209/DCSIGN	Rubella	Antibody variation	2. Haralambieva et al., 2014
RARB	Rubella	Antibody variation	2. Haralambieva et al., 2014
MOG	Rubella	Antibody variation	2. Haralambieva et al., 2014
IL6	Rubella	Antibody variation	2. Haralambieva et al., 2014
BTN3A3/BTN2A1	Rubella	Cellular variation	3. Kennedy et al., 2014
IL10RB/IFNAR1	Rubella	Cellular variation	3. Kennedy et al., 2014
PVR	Rubella	Cellular variation	3. Kennedy et al., 2014
ADAR	Rubella	Cellular variation	3. Kennedy et al., 2014
CD46	Measles	Antibody variation	7. Haralambieva et al., 2015
SLAM	Measles	Antibody variation	7. Haralambieva et al., 2015
IL12B	Measles	Antibody variation	7. Haralambieva et al., 2015
DDX58	Measles	Antibody variation	7. Haralambieva et al., 2015
IFNA1	Measles	Antibody variation	7. Haralambieva et al., 2015
IL2RB	Measles	Antibody variation	7. Haralambieva et al., 2015

IL4	Measles	Antibody variation	7. Haralambieva et al., 2015
IL6	Measles	Antibody variation	7. Haralambieva et al., 2015
IL8RA	Measles	Antibody variation	7. Haralambieva et al., 2015
TLR2	Measles	Antibody variation	7. Haralambieva et al., 2015
TLR4	Measles	Antibody variation	7. Haralambieva et al., 2015
TLR5	Measles	Antibody variation	7. Haralambieva et al., 2015
TLR7	Measles	Antibody variation	7. Haralambieva et al., 2015
VISA	Measles	Antibody variation	7. Haralambieva et al., 2015
TRIM5	Measles	Antibody variation	7. Haralambieva et al., 2015
TLR1	BCG	Less osteitis	[16]. Pöyhönen et al., 2015
TLR2	BCG	More osteitis	16. Pöyhönen et al., 2015
TLR6	BCG	More osteitis	16. Pöyhönen et al., 2015
CD14	Pertussis	IgG antibody variation	[17]. Kimman et al., 2008
TLR4	Pertussis	IgG antibody variation	17. Kimman et al., 2008
TOLLIP	Pertussis	IgG antibody variation	17. Kimman et al., 2008
TIRAP	Pertussis	IgG antibody variation	17. Kimman et al., 2008
IRAK3	Pertussis	IgG antibody variation	17. Kimman et al., 2008
IRAK4	Pertussis	IgG antibody variation	17. Kimman et al., 2008
TICAM1	Pertussis	IgG antibody	17. Kimman et al.,

[16] Pöyhönen L, Nuolivirta K, Vuononvirta J, Kröger L, Huhtala H, Mertsola J, He Q, Korppi M. Toll-like receptor 2 subfamily gene polymorphisms are associated with Bacillus Calmette-Guérin osteitis following newborn vaccination. Acta Paediatr. 2015 May; 104(5): 485-90. PubMed PMID: 25605403

[17] Kimman TG, Banus S, Reijmerink N, Reimerink J, Stelma FF, Koppelman GH, Thijs C, Postma DS, Kerkhof M. Association of interacting genes in the toll-like receptor signaling pathway and the antibody response to pertussis vaccination. PLoS One. 2008; 3(11): e3665. PubMed PMID: 18987746

		variation	2008
TNFRSF4	Pertussis	IgG antibody variation	17. Kimman et al., 2008
TLR3	Meningococcal sero C	Antibody variation	5. O'Connor et al., 2014
CD44	Meningococcal sero C	Antibody variation	5. O'Connor et al., 2014
VDR AA homozygous	HBV	Immune non-responder	6. Grzegorzewska et al., 2014
VDR GG homozygous	HBV	Immune responder	6. Grzegorzewska et al., 2014
HLA-DRA	HBV	Antibody non-responder	[18]. Davila et al., 2010
FOXP1	HBV	Antibody non-responder	18. Davila et al., 2010
C1QB	Yellow fever	Cellular accuracy	20. Querec et al., 2009
EIF2AK4	Yellow fever	Cellular accuracy	20. Querec et al., 2009
TNFRS17	Yellow fever	Antibody responder	20. Querec et al., 2009

Summary

The near future of vaccinomic development is to understand gene signature profiles in individual vaccination receivers based on their genetic and immune polymorphism. Gene signature will be used to guide the development of individual vaccination based on various and individual specific immune response markers, to support personalised vaccinology and to promote novel vaccine development.[19] An excellent example of gene signature in vaccination is the design of the yellow fever vaccine.[20] Here the genes C1QB and EIF2AK4 associated with CD8 T cell responses are targeted with higher accuracy; and the gene TNFRS17 of B cell growth factor is targeted for a predictive signature of

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neutralizing antibody response. Future vaccine development with the advanced tools of vaccinomics and predictive vaccinology will abandon the “one size and dose fit all empiric vaccine approach” and establish personalized vaccinomics with gene signature.

Bibliography