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Journal of Vaccines & Vaccination

Review Article

# Personalizing Vaccination for Infectious Disease in the 21st Century

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## ABSTRACT

Current approaches to vaccination have several underlying assumptions, namely that following immunization most individuals are at similar risk of the disease considered will react immunologically in the same way (with protective antibodies and/or cell-mediated reactivity) with equivalent and minimal side effects and that vaccination dosing and frequency of administration does not vary in the population at large. As a result a widespread delivery of vaccines has been achieved for a number of infectious diseases, with effective control for many of those. It is clear that a weakness of this approach, made manifest with our increasing knowledge of the genomic and proteomic approach to medicine which has come to the fore in the last decade or so, is that it discounts the growing evidence for individual variability in risk; in immune responsiveness; and in response to different doses of vaccine. While this evidence grew from a focus on tailoring individual approaches to cancer therapy, and has revolutionized our thoughts on drug therapy, drug pharmacogenomics and toxicity and the importance of understanding at the individual, not population level, unique responses to treatment, application of the same approach to vaccines for infectious disease has not had a similar attention. Indeed, not only does consideration of individual specific factors challenge a traditional public-health level paradigm of infectious disease vaccinology, and confront newer approaches based on genetically encoded individuality in response to pathogen challenge, but the cost-benefit of such an approach has, to the author's knowledge, not been considered at all. The review below will consider these issues in greater detail, with a final focus on how this might dictate our global responses to emerging infections.

**Keywords:** Personalized medicine; Vaccine development; Immunology of host resistance; Innate immunity; Acquired immunity; COVID-19

## INTRODUCTION

It goes without saying that the development of the field of personalized medicine was fostered by the completion of the (Human Genome Project) and the international HapMap, with further advances then dependent upon new molecular assay tools allowing for high-throughput detection of gene variations, particularly Single Nucleotide Polymorphism (SNP) and linkage disequilibrium maps. This applies even to high-throughput tools needed for the genotyping of SNPs known to be related to drug and xenobiotic metabolism [1-3].

Application of standardized therapies in a number of cancers has shown great individual-to-individual variation in response to treatment. With the advent of immunotherapies, that variability became even more pronounced, reflecting presumably polymorphisms in key immune response genes which in turn lead to heterogeneity in immune responses to biologic manipulation, as well as genetic variability in the expression of target molecules on individual tumors to which immunotherapy was directed [4-8]. Fundamental advances in knowledge of the mechanism(s) responsible for tumor cure were essential before any rationale could be applied in this field [9-13]. More recently however there has been attention paid to other demographics in the population, particularly age and age-associated immune changes (e.g. in natural killer cells; naïve T cells), in altering individual responses to cancer therapy [14]. A more challenging variable, in terms of understanding and incorporation into therapeutic predictions, is the growing evidence that the gut micro biome can influence overall immunity, and may affect immunotherapy of cancer [15].

This notion that a new focus on personalized medicine might represent a paradigm shift in many chronic diseases led to rapid "spill-over" into other fields, including as an example, allergy and autoimmune diseases [16,17]. Systemic Lupus Erythematosus (SLE), a disease with wide ranging clinical symptoms, has an equally heterogeneous biological diversity, and newer investigations on peripheral blood immunophenotyping using flow cytometry and mass cytometry to identify cell subsets and markers associated with that disease heterogeneity, along with transcriptome analysis to highlight molecular networks responsible for disease activity and disease subtype/response to therapy, are contributing to newer approaches [17,18]. Understanding the correlation between risk alleles and the nature of both underlying immune abnormalities and varied drug responses (pharmacogenomics) across populations,

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**Received:** October 16, 2020; **Accepted:** October 29, 2020; **Published:** November 5, 2020

**Citation:** Gorezynski RM (2020) Personalizing Vaccination for Infectious Disease in the 21st Century. J Vaccines Vaccin. S5:005.

as already noted in the approach to cancer therapy, is key to any rationale intervention in autoimmunity and inflammatory disease [19-21].

## UNDERSTANDING THE VARIABLES CONTRIBUTING TO ALTERED VACCINATION IN INFECTIOUS DISEASE

It has long been acknowledged that polymorphisms in a number of immune response genes results in heterogeneity in immune responses to many biologics including vaccines [22]. However, given the success of a traditional public-health level paradigm of infectious disease vaccinology, resulting in the successful eradication of a number of scourges, including smallpox, and good control of many childhood diseases (measles/mumps/rubella/varicella/polio) with a high cost-benefit ration across global societies, little attention has been paid to the potential value of a more individual specific approach to vaccination against infection. This despite broad evidence that there are important genetic differences (e.g. humans HLA Class II controlling human antibody responses) contributing to different responses to Hepatitis B Virus (HBV) and measles virus vaccines [23-25], leading potentially to the documented increased susceptibility to HBV [26,27]. Genetic differences also contribute to sex-related difference in response to vaccines, with women in general mounting an increased antibody response over men [28]; and to more subtle racial/ethnic differences such as the Km/Gm antibody carried by Native Alaskans and Native Americans which had been previously controversially thought to be associated with impaired immune response to polysaccharide vaccine antigens [29,30]. Indeed, even polymorphisms in response to a common drug which alters transcription of immune response genes has been associated with altered response to (cancer) vaccines [31]. The risk of adverse events following a standard vaccination regime has also been linked with genetic predisposition e.g. vaccinia associated pericarditis, occurring an estimated 1:1400 individuals) following vaccination vs. smallpox [32,33], including the risk of febrile seizures following vaccination with MMR vaccine [34,35].

It should be noted that not only HLA-related polymorphisms, which are likely related to recognition of antigenic epitopes on the infection pathogen, but cytokine gene polymorphisms associated with further development of immune responses have proven relevant in infectious immunity [25,36,37]. Gender differences in response to measles and rubella vaccination have also been reported [38-40] for a review of sex related difference in immunity) Moreover, given that we now know that immune responses change both qualitatively and quantitatively with age, with a marked shrinkage in the immune response (T cell) repertoire in elderly individuals [41], along with an expansion of "exhausted T cells with high PD-1 expression [42], it should be no surprise to find that there are wide variations in response to vaccination with age.

Original Antigenic Sin (OAS), a term first used by Francis in 1960 [43] refers to the phenomenon that the shape of on-going immune responses to a persistent/recurrent pathogen (in the case studied, influenza) was "molded" by the initial response made. Thus the majority of influenza virus antibodies in a population showed cross-reactivity to the original (pioneer) strain for that group [44]. Neonatal immune responses are in general more limited in heterogeneity than the adult counterpart, which may in part explain the poor response to vaccination in the former, when using recombinant antigen (not inactivated viral) vaccines, as compared with immunity generated by live virus infection which presumably offers a broader epitope range for immune challenge. The issue of contraction of the repertoire in the elderly in turn then helps explain their generally poorer response to vaccination by contemporary vaccines. Imprinting, the phenomenon whereby first exposure to pathogen shapes all subsequent exposures [45,46], and interference (which explains how antibody to an original strain of pathogen can interfere with antibody responses to subsequently encountered (different) strains) [47] further compounds these age related altered immune responses to pathogens. The contribution to all of these factors in understanding the contemporary approach to influenza vaccination is discussed below. Consideration will they be given as to how this might guide thoughts to developing useful strategies to novel infections and/or pandemics.

## INFLUENZA AS A MODEL FOR POPULATION BASED INFECTIOUS DISEASE CONTROL

Influenza is a major health problem, with in the order of 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths per year world-wide [48]. Young children (<24 months), pregnant women, immunocompromised subjects, individuals with co-morbidities regardless of age, and the elderly all have a higher risk for influenza-related co-morbidities, many of which will lead to death. In healthy children younger than 24 months of age, the risk of hospitalization is comparable to that of high-risk groups, or even higher. Vaccination is the mainstay of protection against disease. A major challenge to an effective vaccination program follows from the understanding that influenza viruses are constantly changing, leading to antigenic drift those results in escape from earlier immune responses. Thus monitoring vaccine efficacy is a key issue in the strategy for mass vaccination. As a correlate marker of vaccine efficacy an immune function which can be shown to be responsible for protection, and is easily measured is used for monitoring (e.g. influenza serum hem agglutination antibody titres, HI), and stringent criteria must be met for licensure of a vaccine. In terms of population responses, a pre-determined increase in titre: e.g. >40 in 18-60 year olds with a 4-fold increase in titre post vaccination and >40% seroconversion in the same group has historically been associated with 50% reduction in influenza risk [49]. However, it is recognized that in the elderly, where standard vaccine therapy is ineffective [50], strict analysis of HI titres may not be as useful in guidance of vaccination, and monitoring of cell mediated immune responses may be more valid predictors of efficacy [51-55]. This is an important issue; since we know that antibody and cell mediated responses are generally directed to different antigenic epitopes. Thus, in the absence of use of live vaccine, or a live attenuated virus vaccine [56] our choice of recombinant material to include in any vaccine on offer must encompass the antigenic determinants likely to provoke the relevant immune response in the population at risk. Current developments in the influenza vaccine field have addressed these issues and use novel methodology to determine responses other than HI tires which are more applicable in other populations [57-60].

Another correlate of the move away from use of live attenuated or whole cell vaccines, which already contain inbuilt adjuvants promoting auxiliary immune stimulation (e.g. bacterial cell wall components; other genetic material including polynucleotides) to the use of purer (recombinant) antigens for safer vaccines, is that there has been an attendant development in the field of novel adjuvants which are now necessarily added to improve efficacy of these newer recombinant vaccines [61,62]. Safety testing of such

adjuvants is also needed, and careful choice, given evidence that different adjuvants may promote antibody vs. cellular immunity [61,62].

## CONCERNS ABOUT AN INDIVIDUAL APPROACH TO VACCINATION

Despite the evidence that improved vaccine efficacy might arise from personalization of the vaccination strategy used, there are considerable practical issues which make this a very difficult task. Screening for individual factors which contribute to vaccinate differently across subgroups will likely add substantial costs to vaccination, although potentially saving other costs (e.g. hospitalization of elderly and other high-risk groups). As already noted, use of personalized vaccines depends on prior knowledge/characterization of genetic influences on immune response, a field still developing and for which no current routine population testing is offered. Pre-vaccine screening for immune status has been considered, but with the exception of the unvaccinated adult with respect to varicella vaccination, where serologic testing in an adult with a negative history of chicken pox is cheaper than vaccination, vaccination is cheaper than testing.

Most vaccines currently used for infectious disease have high immune response rates, and there is concern over the overall cost of achieving small further advances in vaccination uptake following population genetic screening in order to improve the immune response to vaccine for a minority of the population. Careful consideration of the overall costs to health care should a highly susceptible population contract the disease under consideration clearly will play a major role in this determination. In a similar light, screening for an increased propensity to adverse events in subgroups of individuals may foster a drive for general genetic screening.

There is also the practical difficulty of licensure of personalized vaccines. This is less an issue for treating patients with cancer, where development of individualized cancer vaccines lacks the attendant problems facing manufacturers trying to license materials for mass production and distribution. As of now, regulatory bodies require prelicensure testing in animals and humans for all vaccines and for each dose and schedule. It is against such a background that there is a growing interest in the development of a "one-size-fits-all adjuvanted peptide vaccine cocktail", which may prove the way forward for e.g. influenza vaccines, in the not-too-distant future. In such a model, different individuals will respond to different agents contained in the cocktail, which are pre-selected and included based on population-level HLA super type frequencies and age distribution [63].

## PERSONALIZED MEDICINE AND RESPONSE TO NOVEL INFECTIOUS AGENTS, INCLUDING COVID-19

In this final section we will consider the value of the information outlined above in determining global responses to new infectious agents, with a particular focus on COVID-19. At the time of writing (September, 2020) the world is immersed in focus on a pandemic associated with COVID-19 infection. However, even though this is a novel coronavirus infection, our knowledge of past pathogens should be a useful guide to how we approach the problem of developing and using a vaccine. Much of the modeling and thought behind the response to COVID-19 has used as background data on recent coronavirus infections (SARS, MERS) [64,65] and even the global response to the 1918 Flu Pandemic.

Spanish flu, also known as the 1918 flu pandemic, was a particularly deadly influenza pandemic caused by the H1N1 influenza A virus [66]. A second pandemic caused by H1NI was the so-called swine flu pandemic of 2009 [67]. The former lasted about 15 months from spring 1918 (northern hemisphere) to early summer 1919, infected approximately one-third of the world's population at the time (500 million people), and had a death toll estimated to have been anywhere from 17 million to 50 million, and possibly as high as 100 million, making it one of the deadliest pandemics in human history [68,69].

While most influenza outbreaks produce their highest mortality in the very young and the very old, with a higher survival rate for those in between, the 1918 pandemic resulted in a higher than expected mortality rate for young adults. Scientists offer several possible explanations for the high mortality rate of the 1918 influenza pandemic. It has been suggested that the virus was particularly deadly because it triggered a cytokine storm, leading the severe pneumonia (much like thoughts regarding COVID-19 see below) [70,71]. Alternative, or additional socioeconomic features including those associated with malnourishment, overcrowded medical camps and hospitals, and poor hygiene, all exacerbated by the recent war, which likely contributed to bacterial super infection were also likely important in 1918 [68,71,72].

As mentioned repeatedly, without understanding the physiology, immunobiology and genetics of the host response to any infection (in this case COVID-19), health experts are floundering in the dark. In the early phases on the COVID-19 pandemic, effort was focused on PCR testing to assess for evidence of viral infection in symptomatic individuals to obtain some gauge of the prevalence of infection-neglecting the concern that knowledge of infected but non symptomatic individuals may contribute significantly to understanding the disease. Furthermore, the absence, in the early stages, of any serology data recording the numbers infected who developed a measurable immune response, and how that correlated with disease progression, also hindered understanding. An early report from Germany put this, in one local, at a minimum of 14%, but again with no corollary data on symptoms [73]. Global media reports have cited mortality statistics projections from 1% to upwards of 14%, but without any widespread population data, these numbers were simply nonsensical. As a comparator (see data above regarding influenza virus statistics) the SARS corona virus infection, which struck in 2003 had a global fatality rate of 9.6% (12.4% in Canada) [74], but with a relatively restricted number of infected individuals (predominantly person-to-person spread).

Of major concern in COVID-19 is the controversy regarding our understanding of the mechanisms of initiation and spread of the disease? Current dogmatic thinking suggests person-to-person spread, including by aerosols, though there are numerous contradictory data which refute this but are ignored. Not surprisingly then there has been confusion and controversy over the value of using face masks as a method of preventing disease spread, though a recent report in the New England Journal of Medicine indicates it may at least be efficacious in alleviating anxiety [75]. There can be little doubt that fomite spread is an important issue, so advice re hand washing practice of good hygiene practice is paramount [76]. A much more radical alternate hypothesis, based on the available epidemiology, the developing spread of infection across Europe, and sequence data from viral isolates, suggests that the inciting event may have originated in a cloud of dust of cosmic origin

containing a pure culture of the virus arriving in large quantity first over China, and then dispersed through stratospheric transport processes to be deposited on a global scale following prevailing atmospheric drift [77-81]. This "fall-out" of viruses associated with the current COVID-19 crisis is seen as representing a small perturbation of the billions of viruses per square metre per day that fall through the atmosphere, some of which can be recycled from Earth sources [82], but many of which were predicted and discussed in the past by Hoyle and Wickramasinghe [83].

In an interesting recent submission Qu and Wickramasinghe discussed the advantages of scientific "preparedness" to detect the influence of cosmic ray flux, space weather, and the possible introduction of novel bacteria and viruses from the stratosphere [84]. Such organisms have already been detected at heights up to 42 km [85,86], and indeed on the exterior of the ISS orbiting the earth at over 400 Km [87]. Independent measures of the downward flux of viruses in the Sierra Nevada Mountains have ranged from 0.25 x 109 to greater than 7 x 1010 m-2/day [88], numbers which are not easily explained as having originated on the ground [89].

As might be anticipated, there has been intense resistance to this view of the new pandemic (particularly as it argues against the weak evidence for person-to-person transmission as a major focus of the initiation of infection) associated with a long standing scientific resistance to accept hypotheses concerning our possible cosmic ancestry and origins (panspermia) which is discussed elsewhere [78,81,82,90] for more discussion on the role of solar activity and incidence of viral pathogenesis). Nevertheless, almost all so-called experts have supported governments in the imposition of quite draconian measures restricting people's lives and movements unheard of in peacetime, across almost all countries (with perhaps the notable exception of Sweden). The attendant short- and, more importantly, long-term costs to the mental, social and economic well-being, as well as the overall health, of those populations has not been well thought through [91]. It has also been argued that attention to this alternative hypothesis (infection as an "infall event" from the stratosphere) allows for testable scientific predictions, most important of which for future potential emerging infections is that it suggests a pro-active rather than a reactive approach to vaccination strategy. If we accept that newly arriving (on earth) infectious material is already accessible in the stratosphere, then sampling this material should provide advance warning (by 1-2 years) of new "emerging" pathogens on earth, providing substantial lead-time to investigate responses to infection in mammals and development of containment/vaccination procedures.

Such lead time may well be crucial. As is evident from over 40 years of research on influenza vaccination, we are still a long way off providing optimal vaccination regimes for the most vulnerable members of our communities (the young; elderly; and those with multiple co-morbidities). We have little knowledge concerning the biology and host resistance factors of many of our more newly documented infectious agents (Zika virus [92]; Candida auris species [93-95]; COVID-19) [96]. A preliminary report in 108 volunteers (ages 18-60) of immunity in humans following administration of 3 different doses of an Ad5 vectored COVID-19 [97] documented production of both T and B cell immunity (peaking by 14/28d post vaccination respectively) with minimal adverse effects. To date, the correlation of either (or both) of T/B cell immunity with protection following vaccination against COVID-19 remains unknown, and the authors in the study acknowledged that they were unable to predict the protection of the Ad 5 vectored COVID-19 vaccine on the basis of the vaccine-elicited immune responses in this study. There are, however, guiding principles available from previous studies of other coronavirus infections in man, investigating SARS and Middle East respiratory syndrome (MERS) respectively. Here the increases in specific antibodies were temporary [98,99], and declined quickly in patients after recovery, whereas it seems that both specific CD4+ and CD8+ T-cell responses played an equally if not more important role in mouse models of immunity [100,101]. A similar rapid decline of the specific antibody amounts in patients with COVID-19 after recovery has also been recorded [102,103], again consistent with the notion that both specific cellular and humoral immunity may be crucial for a successful COVID-19 vaccine. Note that little data is available even in preliminary form for vaccination of patients in particularly vulnerable groups (elderly; those with other co-morbidities [104]), as is any detailed assessment of the usefulness of different adjuvants in enhancement either/both T cell and B cell immunity [105] or even whether unique T and/or B cell recombinant epitopes might prove a safe but effective route of vaccination for protection [106,107]. It is also pertinent to note that given the fact that COVID-19 (and SARS-CoV/MERS-CoV) targets primarily the respiratory tract, designing a vaccine which induces immunity after intranasal delivery might be an optimal strategy for vaccine development.

As regards development of a more specific COVID-19 vaccine, following engagement of the acquired immune response (B and T cell immunity) over the next 12-18 months, one might ask what would the platform for vaccine development look like? RNA vaccines are rapidly produced, but to date none has been licensed for any viral infection. Splicing a relevant gene into an accepted viral vector is an alternative, and has been used for a licensed EBOLA vaccine [108]. More likely the licensed product will use a recombinant protein of COVID-19, in association with a suitable adjuvant, as this protocol has the best promise of rapid delivery of a licensed vaccine at the volume needed for the global community [109,110]. As discussed above with reference to influenza vaccines, care must be taken to optimize safety and ensure the reagents used do not cause antibody mediated disease enhancement [111-113]. Merging multiple streams of new data and information are improving the rapidity of development of a COVID10 vaccine [114,115], but at the time of writing the prevailing thought is that any vaccine for COVID-19 is still several months away, with risk assessment of vaccines still pending.

In this interim period, is there any approach that can be used (besides drug therapy) to temporize while we await production of a suitable vaccine? It is known that the immune response in mammals is comprised of both an innate and adaptive arm. The latter (T and B lymphocytes) are responsible for immunologic memory, but take some 10-14 days post pathogen exposure to become active. In contrast, protection mediated by the innate immune system, which is the sole immune mechanism for 95% of the species on earth, develops quickly (1-2 days), although it has been argued it does not display immune memory. The latter issue has now been challenged by data which has shown quite clearly that "training" does occur in adaptive responses, which results in an enhanced protection from reinfection (with the same pathogen) and even enhanced immunity to novel (non-tubercular) pathogens [116]. The mechanism(s) involved are thought to involve epigenetic changes (altered DNA methylation; Histone deactylase activity) which results in more rapid gene activation of genes implicated in pathogen responses, as well as an altered cell metabolism. As an example, monocytes

obtained from individuals vaccinated with BCG vaccine have been shown to exhibit enhanced cytokines responses (IL-1β; IL-6; TNFα production) on exposure to other (yellow fever) viral pathogens [117]. This same phenomenon may in part at least be responsible for the observations made some time ago that infant mortality, and even adult mortality, is less in BCG vaccinated cohorts that in non-vaccinated cohorts from the same population [118]. Since the effects of BCG in human experimental subjects have been seen at long times (>12 months), beyond the time expected for an effect mediated by epigenetic changes on mature monocytes, it has been thought that re-programming of myeloid development from bone marrow precursors must also occur, as documented now by [119]. The implications then of using such BCG-mediated training of innate immunity in vaccine development has in turn been discussed elsewhere by Covian [120], and provides the underlying principle behind the ACTIVATE trial in elderly volunteers to assess the contribution of BCG vaccine in decreasing susceptibility to bacterial disease [121]. More recently a BCG-CORONA trial [122] has also been initiated to assess the value of BCG vaccination in reducing health care worker's infection and disease severity during the epidemic phase of SARS-CoV-2 [123].

It has also been suggested that on-going development of human monoclonal anti-COVID-19 antibodies be developed also as treatment regimens, given their now known proven efficacy in HIV infection [124,125]. This has been reviewed elsewhere by Sharun [126,127].

## CONCLUSION

It should be apparent that there are good parallels, drawn primarily from the emerging field of personalized care in cancer therapy, to argue that such an approach will have a major impact in the future treatment of infectious disease. The arguments raised above show that this cannot take place in a vacuum, however, and depend heavily upon improved knowledge of the epidemiology and natural resistance mechanisms in any infectious disease outbreak. Using the contemporary global response to COVID-19 infection, it is clear that attention to such variables have not characterized what has often been a response dictated more by political expediency, and scientific dogma, than by a rationale attention to the emerging facts. Indeed a recent summary of data in exposed but asymptomatic individuals concluded that "SARS-CoV-2-specific memory T cells were detected in exposed seronegative healthy individuals (relatives of confirmed cases), indicative of asymptomatic infection. Remarkably, "93% of 'exposed asymptomatic individuals mounted detectable T cell responses to SARS-CoV-2 despite only 60% of cases being seropositive. This suggests that asymptomatic infections may be more common than current data suggest and that immunosurveillance through antibody testing alone may underestimate infection prevalence or population immunity. The presence of SARS-CoV-2-specific T cells in the majority of convalescent patients is a promising sign that infection may give rise to immunity, but whether these T cells afford protection from reinfection remains to be tested".

While the hope exists that an effective vaccine (for some) may emerge from current studies with the candidate vaccines now under consideration, it is clear that more attention to the role of a bolstered innate immune response, and the value of adjuvants as triggers of the latter, along with careful analysis of the role of the nature (and degree) of any acquired resistance mechanisms which may be effective, will be paramount to success across populations, and particularly for those at greatest risk. It is wise to remember indeed that the universal argument made in favor of mass quarantine in the early stages in virtually all affected countries was this notion that we must protect the vulnerable (elderly) and those with co-morbidities who were at greatest risk vaccination strategies must do likewise.

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