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Review Article

COVID-19 vaccine-elicited immune mediators and their contribution to protective immunity

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ABSTRACT

SARS-CoV-2, a highly transmissible virus triggered the COVID-19 pandemic inflicting devastating impact on public health and global economy; thus, the development of a vaccine was deemed the most efficient strategy. The immune system is a network of specialized cell types that interacts with cytokines to orchestrate protective responses. Until recently, investigators only evaluated vaccine efficacy with an emphasis on secreted antibodies, despite advancements in vaccinology no well-confirmed immunological correlates of vaccine-induced protection have been recognized. Technological and conceptual advances in cell-mediated immunology have resulted in numerous novel immunological signals, which could function as classifiers for vaccine-induced protection. Cytokine responses are essential for triggering and retaining humoral responses, which could potentially impact vaccination efficiency, thus, profiling might uncover vital information on the indicators of vaccine response and long-term protective variables. This integrated immunological approach to vaccine response provides a broader perspective and ensures an improved comprehension of the pathways and mechanisms involved. Here we aim to summarize the mechanism of action of the different vaccines developed and examine several immunological mediators associated with SARS-CoV-2 immunization. We also provide insights, on new possibilities correlating with vaccine-induced immune responses and their effectiveness in defining protective immunity.

Keywords: SARS-CoV-2, Vaccine, Humoral immunity, Cytokines, Cellular immunity

INTRODUCTION

COVID-19, which triggered the global pandemic in 2020 affected approximately more than 500 million individuals, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded RNA virus belonging to the genus Betacoronavirus.[1] With the surge in the infectivity rate due to its rapidly increasing genealogy, characterization of the 13 different variations was warranted. Some of the major variations of concern (VoC) included Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529), with Delta and Omicron being the most problematic.[1] Symptoms vary from self-limiting to mild, and occasionally advancing to severe conditions exhibiting acute respiratory distress syndrome (ARDS). The type of interaction between the pathogen and host in any disease determines the immune response; when this response shifts towards disequilibrium, it contributes to disease pathophysiology.

Furthermore, the host immunological response to infection influences the variability in clinical outcomes. The phrase 'cytokine storm' refers to the uncontrolled secretion of cytokines that leads to immunopathological responses. In addition to eliciting an adaptive immune response, SARS-CoV-2 infection also induces uncontrolled cytokine production during severe conditions. Immune mediators such as IFN-α, IFN-β, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, IL-33, TNF-α, and TGF-β secreted by cells are known to be altered and are associated with disease pathogenesis. These mediators have crucial, albeit somewhat inconsistent effects on maintaining host immunity against COVID-19.[2,3]

As of April 2024, global infection count is over 70,47,53,890 and with a mortality count of 70,10,681 individuals.[4] Consequently, researchers have focused on developing viable interventions and medications to combat this pandemic. This culminated in the development of numerous vaccines. Significant improvements have been achieved in managing the COVID-19 pandemic; nevertheless, much of the effort remains focused on minimizing infection and disease severity by vaccination (approximately more than 13 billion vaccine doses have been administered), which has occasionally led to some negative repercussions.[5,6] Unfortunately, numerous novel variations in the Omicron variant have recently emerged, leading to breakthrough infections. These adverse reactions and breakthrough infections have stimulated persisted research on these vaccines. Cytokine-mediated cellular immunity is another facet of host response to immunization which has been associated with both vaccine effectiveness and adverse effects in various infections including smallpox and influenza.[7,8] The significance of cytokines in COVID-19 immunization remains unexplored. Recently, system biology methodologies have been used to characterize the molecular determinants of COVID-19 vaccination responses. Despite the latest developments in COVID-19 vaccine production, findings on the cellular response generated by vaccination are scarce compared to humoral response data. Understanding the relevance of cytokine-mediated cellular immune responses following immunization is vital.[7] This review provides a comprehensive summary of different vaccines available and their mode of action. Finally, we discuss the systemic cytokine secretion in post-COVID-19 immunized individuals and role in developing protective immunity.

VACCINE VARIATIONS

The pandemic necessitated an immediate initiative to develop effective vaccines for the SARS-CoV-2 infection. In this unprecedented occurrence, as the transmissibility of the infection was in unparalleled numbers, numerous vaccination platforms had been launched. Several of the possibilities investigated were based on conventional vaccination techniques, such as non-replicating and replicating vector-based or inactivated vaccines. Others adopted an innovative and promising platform, such as nucleic acid-based messenger RNA (mRNA) vaccines, which provided the genetic information essential for synthesizing the antigen rather than the antigen itself. In this section, we briefly discuss some crucial aspects of a few groups of vaccines, such as Covishield (ChAdOx1 nCoV-19, or ChAdOx1), Sputnik V, Covaxin (BBV152), BNT162b2, and mRNA-1273 based on mechanism of action, its efficacy against different SARS-CoV-2 variants, and the effectiveness of heterologous vaccination.

MECHANISM OF ACTION

Human adenovirus non-replicating vector-based vaccines

ChAdOx1 is a vaccine based on genetically modified adenovirus developed in cooperation between the University of Oxford and AstraZeneca, moreover it was assembled by The Serum Institute of India, which goes by the name Covishield. It is composed of recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the full-length wild-type spike protein along with N-terminal tissue plasminogen activator (tPA) signal sequence. These signal sequences are essential for host interaction and transporting spike protein to the cell surface. ChAdOx1 is one of the most extensively disseminated COVID-19 vaccines due to its low cost and stability in typical refrigerated conditions.[9] After invading cells, adenovirus employs host proteins to synthesize the spike protein, which is recognized by helper T cells and stimulate B cells to proliferate and produce antibodies against them.[10]

The Sputnik-V vaccine, often known as SVV, is developed according to adenovirus based-vector technology and is the first officially registered COVID-19 vaccine.[10] This vaccine is designed using two independent human adenoviral vectors (Ad 26 and Ad 5), which is associated with more pronounced and sustained immune response than other vaccines utilizing these identical vectors. The method resembles that of AstraZeneca where the adenovirus infects the cells with an engineered DNA fragment, which then synthesizes protein homologous to spike protein of the coronavirus that is capable of stimulating adaptive immune response to protect individuals from breakthrough infections.[10]

Inactivated coronavirus vaccines

Covaxin, additionally referred to as BBV152, was developed by the Bharat Biotech firm in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology, was the 2nd most administered vaccine in India. The vaccine employs inactivated viral technology, which is incapable of replicating and instead instructs the immune system to generate a protective reaction to infection. The viral

component utilized exhibited 99.7% strain similarity to the Wuhan Hu-I strain.[11]

BBV152 is a whole-virion β-propiolactone inactivated COVID-19 vaccine with IMDG an agonist molecule adsorbed to alum that acts as an adjuvant. This combined formulation activates both cell and humoral-mediated immune response. Once within the human system, inactivated viruses are engulfed by antigen-presenting cells, which phagocytose and present fragments to immunocompetent cells, such as helper T cells, which upon activation secretes cytokines that aids in recruiting additional immune cells, thus enhancing the immune response. Concurrently, another type of immune cell, i.e., the B cell, proliferates upon activation and produces antibodies that specifically binds with the spike protein of the virus thereby aiding in viral neutralization and clearance.[11,12]

mRNA vaccines

Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) have analogous approaches to activation. Lipid nanoparticle transport system is utilized to deliver the nucleoside-modified mRNA that codes for SARS-CoV-2 spike protein with additional transmembrane protein necessary for anchoring to the host cells. These two types of immunization induced robust humoral as well as cell-mediated immune response to the spike protein. The vaccine's distinctive features comprise an efficient delivery system, as well as utilizes modified nucleotides which suppresses early activation of interferon-associated genes.[13] After intramuscular injection, immune cells interact with lipid-nanoparticles and release the mRNA into the cytoplasm which then is translated to viral S protein. T cells upon activation secret IL-2, IL-4, and IL-5, which aids in the proliferation of B and memory T cells, thereby amplifying the overall immune response.[10]

EFFICACY AGAINST DIFFERENT SARS-COV-2 VARIANTS

Since its first outbreak in December 2019, SARS-CoV-2 has developed over ten mutant strains. Five of these variances alpha, beta, gamma, delta, and omicron were deemed to be more transmissible with limiting neutralizing capacity and/or more fatal than the original Wuhan strain, and was acknowledged as VoC by World Health Organization (WHO).[14] Some of the variations' modification have been associated with increasing transmissibility and likelihood of bypassing the protective effects of vaccination or past infections. In 2022, omicron surpassed the other variations to become the most prevalent circulating variant exhibiting more pronounced immune evasion capacity, thereby having a more significant impact on the efficacy of immunizations and monoclonal antibody therapies. Although transmissibility of omicron variant was the highest, Delta strain exhibited highest level of severity in comparison to other variants.[14,15]

Table 1: Characteristics of different anti-SARS-CoV-2 vaccines.

	Covishield	Sputnik	Covaxin	BNT162b2	mRNA-1273
Mechanism of action	Viral vector Vaccine (Adenovirus-Chimpanzee ChAdOx1)	Viral vector vaccine (Ad26 and Ad5)	Inactivated vaccine	mRNA	mRNA
Antigen	Spike protein	Spike protein	Whole virion inactivated corona virus	Spike protein	Spike protein
Side effects	Pain at site of infection, fever, myalgia, Fatigue, headache, rare thromboembolic events, blood clots, thrombocytopenia, and pulmonary embolism.[27,10]	Fever, chills, arthralgia, myalgia, sore throat, nasal congestion, weakness, malaise, headache, pain, swelling and redness at site of injection. Less common adverse events, nausea, anorexia, enlarged lymph nodes, confusion and syncope.[28]	Pain at site of injection, fever, headache, nausea, vomiting, myocarditis, bell's palsy.[29]	Pain at the site of injection, fever, chills, fatigue, myalgia, local swelling, headache, arthralgia, itching, lymph nodes swelling, diarrhoea. Less common adverse event, allergic reaction, thrombocytopenia, myocarditis, and anaphylaxis. [10,30]	Pain at the site of injection, fever, myalgia, chills, headache, and bell's palsy.[9,10]
Dose	2 dose regime-84 days apart	2 dose regime-21 days apart	2 dose regime-28 days apart	2 dose regime-21 days apart	2 dose regime-28 days apart

Continued.

	Covishield	Sputnik	Covaxin	BNT162b2	mRNA-1273
Efficacy Overall	74%[16]	91.6%[19]	29%-78% [31]	95%[21]	94.1%[22]
Alpha	74.5% [17]	95%[32]	77.8%[12]	87%-93.7%[17,33]	100%[22]
Beta	62%[33]	-	-	72.1%[33]	96.4%[22]
Gamma	41% [33] (1dose)	-	-	63%[33]	89%[33]
Delta	67% [17]	90%[19]	65.2%[12]	40.5%-88% [34]	76%-84.8% [34]
Omicron	48.9%[33]	87.6%[20]	-	65.5%[35]	85% (post seven months-55%)[19]

The overall estimated efficacy of the AstraZeneca vaccine was 74.0%, along with, among individuals aged 65 and above, effectiveness was up to 83.5%.[16] In early clinical research, the AstraZeneca (AZ) vaccine was demonstrated to have been more efficient against severe conditions, exhibiting 100% effectiveness. Additionally, efficacy dropped from alpha variant to delta reaching up to 67%.[17] Moreover, shen et al additionally observed that elderly vaccinated individuals manifested delayed activation of immune response.[17]

Similarly, Covaxin also demonstrated heightened effectiveness towards symptomatic condition in comparison to asymptomatic condition, nonetheless its effectiveness reduced to 65.2% for delta variant.[12] Studies on immunological responses to Covaxin immunization demonstrated comparable neutralization capacity for vaccinated and recovered individuals against delta variants.[18]

Sputnik V exhibited an overall efficacy of 91.6% after phase III with 90% efficiency against delta variant, additionally it maintained its neutralizing effectiveness against alpha, beta, and two different categories of delta variant.[19] In research conducted in Russia during the omicron wave, individuals with one dosage exhibited around 85.9% effectiveness in preventing COVID-19 hospitalization. Moreover, it was 87.6% and 97% for those who took two or more doses respectively, additionally it also highlighted high effectiveness against severe forms than non-severe forms of infection.[20]

Polack et al observed that among 21,720 immunized individuals with two doses of BNT162b2, overall effectiveness against infection was 95%.[21] Comparable to BNT162b2, mRNA-1273 is another type of mRNA-based vaccine exhibiting 94.1% overall efficiency against the wild-type strain. Real-time data on the vaccine efficacy against symptomatic alpha and beta strain from individuals in Qatar reported 100% and 96.4% efficacy, highlighting strong effectiveness between the two variants.[22] Based on clinical evidence, upon immunization by mRNA-1273, approximately about 55% showed positive neutralization activity against omicron post seven months.[23] Similarly, Gram et al observed, effectiveness against mRNA vaccine for elderly individuals to be around 90.7%, 82.3%, and 39.9% against alpha, delta, and omicron variant respectively, and effectiveness diminished post several months of immunization, proposing third dose is beneficial for prolonged immunity.[24]

Additionally other researchers also demonstrated that sera from naïve or recovered vaccinated patients with two doses of mRNA vaccine exhibited diminished neutralizing activity against the omicron variant post six months. Similarly, another group administered with Sputnik V-vaccine showed an 8.1-fold reduction in neutralizing antibody titters to the omicron variant. Hence hypothesizing differing variety of vaccine necessitated for three dose regime modification for more effectiveness against recently discovered variants.[25,26]

EFFECTIVENESS OF HETEROLOGOUS VACCINATION

In multi-dose vaccination series, patients typically are administered the same vaccines for each dose. Alternatively, an advanced approach is utilizing heterologous prime-boost vaccination methodology which involves administering successive doses of different vaccines containing the same antigens. In the case of COVID-19, this refers to a separate vaccination for the second dosage of the two-dose regimen or for the booster dose. Previous research has found that heterologous vaccines can be more immunogenic while providing enhanced immunity. However, it was initially ambiguous if heterologous immunizations provided superior protection against SARS-CoV-2. Naito et al showed that in patients who were primed with two dose regimes of BNT162b2, subsequently dosed with mRNA-1273 resulted in significantly higher anti-spike IgG antibody responses than homologous immunization of BNT162b2.[36]

Investigations on vaccinated subjects with heterologous regime demonstrated that priming with ChAdOx1 followed by an mRNA vaccine (BNT162b2) produces enhanced immunogenicity and more potent humoral immunity than homologous ChAdOx1 vaccines against different VoC such as alpha, beta, and gamma.[37] Similarly, multiple studies reported enhanced levels of IFN-γ positive T-cells and CD8 T-cell levels, along with increased humoral response post heterologous

immunization; thereby conferring better protection and indicating heterologous immunization provides more effective overall protection.[38,39] Another investigation with different mRNA vaccine demonstrated that a second dose with mRNA-1273 following ChAdOx1-priming, boosted the response by enhancing binding affinity and reactogenicity to the variants, thus resulting in more extensive neutralizing antibody titters and memory B cell response thereby manifesting more heightened immune response. In retrospect, humoral response to both homologous and heterologous immunization regime failed to neutralize the omicron variant. This limitation may be due to the increased frequency of non-neutralizing antibodies to neutralizing antibodies.[40]

Another study analysing combinational regime between viral vector and mRNA-based vaccine observed enhanced antibody titre levels.[41] As demonstrated by Ndzouboukou et al, they reported that priming with different kind of vaccine enhanced the humoral and cell-mediated immune response. Furthermore, they also found stronger response to heterologous immunization when employing a viral vector-mRNA sequence for beta and delta strain but contrasting results were observed for the omicron variant.[42] Contrary to favourable outcomes of utilizing heterologous regime for immunization, a group of researchers from Bangladesh reported even though heterologous immunization elicited a more robust immune response during the initial stages, subsequent wanning of vaccine-induced immunity was observed. Moreover, durability was comparable to that observed in homogeneous regime.[43]

In summary, these research gives conflicting insights on heterologous vaccines as well as an association between immunogenicity and effectiveness. More extensive studies are necessitated to design a flexible guideline which incorporates the optimal combination, order and account for varying immune response across the demography.

CYTOKINE SECRETION POST-IMMUNIZATION

Several studies have shown that both the number of IFN-γ-secreting cells and the concentration of serum IFN-γ increased significantly from baseline after COVID-19 vaccination, emphasising their TH1-biased immunological profile. On the same context, a study completed by Ewer et al reported that on day 7 post of 1st dose of ChAdOx1nCoV-19 immunization, IFN-γ and IL-2 expression significantly increased with slight enhancement of IL-10 expression, indicating a predominant TH1 skewness.[44] Elevated levels of pro-inflammatory cytokines such as IL-6 and IL-1β after 1st dose of immunization by ChAdOx1 were one of the reason of adverse events, rather than modulation of the humoral response. On the contrary, adverse events post priming by BNT162b2 was due to the vaccine-induced response.[45] Similarly, preliminary observations in our laboratory indicated that on the 21st day post Covishield immunization, a significant increase in IL-15, IL-12p70, IL-1β, IFN-γ, and TNF-α expression levels were observed. These findings imply a preponderantly TH1 immune response elicited upon vaccination (unpublished data). Tripathy et al reported similar pattern of T-cell response skewness upon priming with both adenoviral and inactivated vaccine platforms. Additionally, Covishield primed individuals exhibited diminished levels of IL-1β, IL-6, and IL-4, whereas those primed with Covaxin showed reduced levels of IL-5 and IL-7, suggesting their specific role in vaccine-induced immunity.[46] Rakshit et al studied the link between BCG re-vaccination and subsequent COVISHIELD vaccination on the immunological response. The results demonstrated that heterologous vaccination improved vaccine-induced Ab and memory T-cell responses. Prior BCG vaccination lowered the threshold level imperative for T-cell activation, thereby enhancing the secretion of IFN-γ, TNF-α and IL-2, with fluctuating expression of IL-17 and IL-10. Another intriguing feature was that a more significant response was observed in patients with BCG reactivation for both Wuhan and Delta strain.[47] Similarly, to analyse the long-term efficacy of sputnik V numerous cytokines profiles were checked on days 0, 21, and 42 post priming. Few of the cytokines comprising IL-1α, IL-10, IL-12p70, IL-2Ra, IFN-α2, and GM-CSF, remained upregulated till day 42. In contrast, some of the cytokines, such as IL-1Ra, IL-2, IL-4, IL-17, CXCL9, CXCL10, IFN-γ, TNF-α, and TNF-β, were downregulated in vaccinated people when compared to baseline levels. Notably, primed-induced modulation of inflammatory mediators mirrored cytokine profile with convalescent phase of COVID-19 patients. Additionally, T cell response remained for approximately seven months indicating that the vaccine had a long-term impact on the immune system.[48]

Multiple studies evaluating cellular response upon priming with inactivated vaccine consistently support the TH1 skewness. A study conducted in Chennai, concluded that post booster immunization with Covaxin, elevated levels of IFN-γ, IL-2, TNF-α, IL-17A, IL-6, IL-12, IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, IL-3, IL-7, CCL4, CXCL1, CXCL2, CX3CL1 were observed. Elevated cytokines and chemokine titres indicated protective response due to TH1 biasness, although some of the TH2 variables stimulated might be due to components present in the vaccine formulation, thereby triggering non-specific response. More extensive research is necessary for comprehending the role of these responses to human health.[49] Additionally, Sun et al reported more pronounced elevation of IL-4, IL6, IL-2, IL-10, TNF-α, and IFN-γ in individuals with elevated antibody titres as compared to those displaying lower humoral responses, suggesting an association between antibody-mediated immunity and cellular response.[50]

Data from Sahin et al demonstrated increased titres of IFN-γ and IL-2 by day 29 post priming with the BNT162B2 vaccine, followed by gradual declining and

stabilization by day 85. In contrast, diminished levels of IL-4 expression have been reported, leading to the robust expression of TH1 cells. Additionally, post vaccinated individuals reported more pronounced expression of cytokines than individuals recovered from COVID-19 infection.[51] Another study on 63 individuals to evaluate early response to BNT162B2 vaccine reported that, out of the 41 analytes, only 19 had any significant modulation of which indicators such as IL-15, IFN-γ, IP-10/CXCL10, IL-6, and TNF-α were significantly upregulated post priming by two doses, indicating longer-lasting vaccine effects. The correlation of IL-15 and IFN-γ with antibody levels culminated into hypothesizing these indicators to be markers of effective humoral development to immunization.[52] Rosati et al quantified serum cytokines which displayed transient modulation post three dose of priming. IL-15 and few inflammatory and anti-inflammatory mediators such as IL-8, CCL22, eotaxin, and IL-16 remained elevated, indicating a long-lasting response highlighting their contribution in innate response as well as in shaping of sustained humoral response.[53] Another group of researchers, highlighted elevated IL-1 and IL-6 expression levels with contradictory trend for IFN-α expression levels hypothesizing towards a more controlled stimulation. This discrepancy to previous analysis might be attributed to implementing different methodologies. Ultimately, they concluded that immunization resulted in long term protection by incorporating both innate and adaptive immune response.[54] In another study, to evaluate adverse events associated with immunization, expression of TH1 and TH2 cytokines were analysed. They reported elevated IFN-γ and IL-5 levels in mRNA-1273 induced response when compared to BNT162b2. The enhanced expression of these inflammatory mediators following immunization with mRNA-1273 reflected a higher probability of adverse events.[55] Konnova et al reported post priming with BNT162b2; IL-15, IL-18, PIGF, and CRP are probable indicators which are able to predict with more than 80% accuracy of which patients had higher probability of having breakthrough infection.[56] Further confirmation of heterologous immunization with mRNA-based vaccine and reactivation with BCG leading to heightened immune response was demonstrated by Martinez et al they reported that at day 30 of post 2nd dose of immunization IL-1β, IL-4, IL-6, IL-12p70, IL-13, IL-18, IFN-γ, GM-CSF, and TNF-α were upregulated when compared to homologous vaccinated group.[57]

To evaluate the vaccine-induced inflammatory response Jiang et al demonstrated a comparative analysis between adenoviral-vector and mRNA-based vaccine platform wherein they observed a more pronounced effect on interferon and pro-inflammatory response following adenoviral-vector vaccination, suggesting a more long-lasting adaptive response when compared with mRNA-based vaccines.[58] Another study on comparative analysis of cellular response post immunization using inactivated and mRNA-based vaccine platform demonstrated a more robust induction of IL-2 and IFN-γ, highlighting enhanced TH1 skewness in inactivated primed PLHIV individuals.[59] Similarly, another group of researchers evaluated the comparative profile of T and B-cell response following priming with different vaccine platform including adenoviral-vector and mRNA-based vaccine. They reported immunization with adenoviral-vector vaccine elicited robust T-cell response, whereas lower B-cell response was observed when compared to individuals primed mRNA-based vaccine.[60]

This discovery of heterologous immunization wherein exploiting different vaccine platform provides an alternative option to obtain swift and more effective protection against the new variants. However as previously stated different strategy elicit different immune signature, extensive research is required for the optimal sequence of the vaccine administration to fully harness their potential in inducing robust protective immunity.[60]

CONCLUSION

The different categories of vaccination, induced significant TH1 and proinflammatory cytokine responses which exhibited positive correlation with humoral response. While these cytokines are physiologically active molecules, they are an indispensable component of the development of protective and long-lasting immunity, inevitably sometimes they are multifaceted, as may be responsible for adverse reaction post vaccination. A broader understanding of the immune response elicited by these vaccines to coronavirus could assist us in monitoring vaccine effectiveness along with uncovering the intricate balance between immunogenicity and reactogenicity.

The present accessible studies have a number of limitations that require further research, including: lack of functional studies of inflammatory mediators; a narrow focus on typical cytokines; studies focused solely on cytokine secretion and not the origin; data analysed over a small sample size; oversight in considering the heterogenicity of the samples; few long-term follow-up data and limited data available on uncommon vaccine types. In order to conceptualize an efficient vaccine with effective antibody production, we must have an improved understanding of both the humoral and cellular immune responses to the vaccination. Additionally longitudinal studies must be undertaken with different ethnic groups which is imperative for consolidating our current comprehension in optimizing the vaccine strategies. This information might be acquired via the application of system biology techniques to the study of pathogen biology and vaccine response. Furthermore, any inflammatory mediator correlating with adverse outcomes subsequent to vaccination must be extensively examined to uncover the molecular basis of the associations. Results of these researches have the potential to optimize present vaccine or aid in driving the design of next-generation vaccine which takes into account of our enhanced

knowledge of individual variability among vaccine recipients.

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