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Changing Face of Vaccination in Immunocompromised Hosts

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Abstract Infection prevention is a key component of care and an important determinant of clinical outcomes in a diverse population of immunocompromised hosts. Vaccination remains a fundamental preventative strategy, and clear guidelines exist for the vaccination of immunocompromised individuals and close contacts. Unfortunately, adherence to such guidelines is frequently suboptimal, with consequent missed opportunities to prevent infection. Additionally, vaccination of immunocompromised individuals is known to produce responses inferior to those observed in immunocompetent hosts. Multiple factors contribute to this finding, and developing improved vaccination strategies for those at high risk of infectious complications remains a priority of care providers. Herein, we review potential factors contributing to vaccine outcomes, focusing on host immune responses, and propose a means for applying modern, innovative systems biology technology to model critical determinants of vaccination success. With influenza vaccine in solid organ transplants used as a case in point, novel means for stratifying individuals using a host "immunophenotype" are explored, and strategies for individualizing vaccine approaches tailored to safely optimize vaccine responses in those most at risk are discussed.

Keywords Vaccination · Transplant recipients · Immunomodulation · Individualized vaccine strategies · Mathematical models · Surrogates of vaccine efficacy · Systems biology · Computational models

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Introduction: Current Status of Vaccination in Immunocompromised Hosts

Infectious morbidity and mortality remains a perpetual threat to a diverse array of immunocompromised patient cohorts [1, 2]. Such groups are disproportionately affected by infection, which can accelerate or precipitate adverse disease processes, positioning vaccination as a key intervention [3]. "At-risk" cohorts are many and include the elderly, neonates, pregnant women, recipients of haematopoietic stem cell or solid organ transplants (SOTs), HIV-infected patients, recipients of the myriad of cytotoxic chemotherapies or biologic therapies, and individuals suffering from comorbid conditions with immunosuppression as a consequence (e.g., obesity, diabetes mellitus, end-stage organ failure, primary immunodeficiencies, autoimmune diseases) [4-8].

Variability of the Immune Response

The observed "phenotypes" of immunosuppression are highly diverse with regard to severity, the specific immunological

signaling cascades involved, and the resulting functional deficits. Therefore, patients from such cohorts merit an individualized approach to addressing the specific "type" of defect to mitigate the negative consequences of infection where possible. Medical interventions to prevent infection take many forms, including the use of prophylactic antimicrobials [9], preemptive monitoring for the emergence of an infection [10], and most important, vaccination. Since first employed as a technique, vaccination has evolved into a powerful strategy for preventing and, in some cases, eradicating human diseases [11-13]. As is discussed later in more detail, "at-risk" populations consistently generate vaccine-specific immune responses that are considerably weaker than those of healthy immunocompetent individuals. Optimizing vaccination by using personalized strategies based on clinical, laboratory, and even computational data may help to select patients at risk for vaccine failure and specifically tailor vaccination approaches.

The broad principles of vaccination for prevention apply equally to all the risk groups listed above. After considering the immunosuppressive conditions, vaccinations should be optimized as early as possible following initial engagement of the individual with the health-care system and repeated as recommended [14, 15•]. Additional protection can be achieved via recommendations to vaccinate family members and health-care workers [14, 15•]. Despite the existence of clear guidance, there remains considerable variability in clinical practice, with many unfounded concerns continuing to undermine optimal vaccination [16, 17].

From an immunological perspective, mounting an efficient and protective vaccine-induced immune response involves a highly complex interplay of numerous cellular and noncellular immune components. Following vaccination of healthy volunteers, it was shown that in peripheral blood mononuclear cells and plasmablasts, several hundred gene-transcripts were significantly altered in their expression [18, 19]. Additionally, the intricate orchestration of the immune response is dependent on the cytokine microenvironment created by migration of activated cells (e.g., transfer of activated monocytes from muscle to lymph nodes), as well as host single nucleotide polymorphisms modulating individual signaling pathways [20, 21•, 22-26]. Even more complexity is added by immunosenescence [27-29], hormonal differences between genders, circadian and monthly hormonal shifts [30, 31], specific vaccine-related differences (type of application [32], adjuvant use [33]), and types of pharmacologic immunosuppression [34, 35]. All these factors combine to generate a complex biological system. Differences arising in any of these factors may account for the high heterogeneity of vaccine-induced immune responses, providing a rationale for examining determinants more critically to identify the fundamental components of vaccine success—in particular, those pertaining to immunocompromised individuals.

Surrogates of Vaccine-Induced Immune Response

Convention directs that antibody production is the primary measure of vaccine efficacy and correlates with clinical protection via activity to neutralize pathogens or pathogenic toxin in an extracellular state. This dependence on antibody is widely debated, and recently the importance of cell-mediated immunity after vaccination has been proposed [36].

Clinical protection has been correlated to adequate levels of antibody production for various reasons. First, neutralizing antibodies are capable of inhibiting infection [37-39]. Second, antibody titers specifically associated with protection from infection have been defined—for example, influenza seroprotection with a titer above 1:40 or seroconversion with a greater than fourfold pre- to postvaccine titer increase [40]. Indeed, meeting such humoral targets heavily influences vaccine design, which primarily seeks to induce an antibody response.

Inactivated subunit vaccines appropriate for use in immunosuppressed hosts such as polysaccharide, protein, or naked DNA vaccines are safer, but less immunogenic and reactogenic [41, 42]. The induced immune response against such vaccines predominantly targets structural proteins, which represent ideal targets for antibodies. Nonstructural proteins, however, are not fully expressed and are, thus, immunologically neglected. Indeed, during "natural" infection, nonstructural proteins may act to induce a potent cytotoxic T-cell response, and it is highly likely that the development of a robust protective response requires more than antibodies alone [43]. Live vaccines in use, although contraindicated for the most part in the immunocompromised, represent an ideal stimulus. They provide both structural and nonstructural antigens and generate broad, robust host responses and durable protection against infection. In this context, antibody production represents but one quantifiable outcome of a highly complex process.

Cellular-based immune assays exist, which can provide more detailed information on the complex interaction of dendritic cells, monocytes, and T- and B-cells. However, measurements of activation markers on cells and intracellular cytokine production or monitoring of cytokine expression profiles requires specific laboratory equipment, is labor intensive, and has not been established in routine clinical settings. In reality, the true correlate of protection remains undefined and is likely to vary on the basis of the pathogen and host–pathogen interaction [36].

In this review article, we will utilize SOT recipients and influenza vaccination as a model to address key issues pertaining to vaccination in immunocompromised hosts. Indefinite immunosuppression and the present reliance on annual influenza vaccination considerably undermine the level of protection that can be achieved. Concluding, we will address potential future strategies for monitoring vaccine responses, applying a "systems biology" approach to advance personalized vaccination.

Influenza Vaccine in Solid Organ Transplant Recipients

In SOT recipients, higher morbidity and mortality rates, as compared with healthy individuals, have been reported during infection with influenza [1]. Specifically in lung transplant recipients, influenza may cause bronchiolitis obliterans syndrome and allograft rejection after lung transplantation and, thereby, reduce graft survival significantly [44-46]. Since the H1N1 pandemic of 2009, influenza vaccine responses in SOT recipients have been extensively characterized. Across different populations and different administration protocols, it was clear that seroprotection and seroconversion to influenza vaccine lagged considerably behind rates observed in the immunocompetent [47-49]. Quoted rates of seroprotection range from 20 % to 60 % [50-53]. Thus, current influenza vaccine practices would seem to be inadequate, most notably in individuals at risk. Influenza vaccine suffers from the need for annual administration and annual antigen adjustment guided by prevailing or predicted antigenic strains. This limitation is further heightened by administration to patients under active immunosuppression, which acts to compound a lack of immunogenicity.

Vaccine-Induced T- and B-Cell Responses After Transplantation

Dissecting the pathways from antigen recognition and delivery through uptake (by antigen presenting cells) and presentation to T-cells directing cell-mediated and humoral immune responses positions dendritic cells at the crucial interface between innate and adaptive immune responses. Adequate protection against intracellular pathogens may also be more reliant on cell-mediated responses, and CD4 help itself is integral to robust B-cell responses. The interplay between key cellular components is complex and is outlined in Fig. 1. Humoral responses aside, influenza vaccine has been shown to induce potent influenza-specific CD4 T helper cells (Th1 and Th2) and T follicular helper cells (T_{FH}) [54, 55]. Indeed, McElhaney et al. proposed that cytokine expression profiles and T-cell proliferation in response to Influenza antigen was, in fact, indicative of protection in elderly adults [56]. Likewise in a HIV cohort, the baseline frequency of naïve CD4 T-cells correlated directly with seroconversion. Interestingly, this frequency of naïve T-cell populations was inversely correlated with age [57]. Thus, baseline integrity of immune cell populations significantly determines vaccine outcomes, and this effect likely magnifies with age. Th2 and T_{FH} cytokines in particular are important cofactors for successful vaccination, since these cytokines are critical for B-cell activation and stimulation [58-61, 62••, 63, 64]. Although Th1 and cytotoxic T-cell responses are induced during vaccination [65], their frequency and function has not been consistently linked to antibody induction [66]. Thus, the critical determinants of vaccine responses and clinical protection have yet to be conclusively determined, and in immunocompromised hosts in particular, quantitative antibody measurements are an imperfect gauge.

Vaccine recipients can be broadly clustered into three groups based on their antibody responses, which, in turn, are dependent on respective helper T-cell cytokine expression and the resulting B-cell activation states:

1. patients with high baseline seroprotection (already seroprotected, no formal seroconversion achievable, memory phenotype),
2. patients with inducible seroconversion (pre- to postvaccine >4-fold antibody increase, priming/naïve phenotype), and
3. nonresponsive patients with low seroprotection and no seroconversion (anergic phenotype).

The Impact of Immunosuppression on Vaccine-Induced Immunity

Immunosuppressive drugs significantly decrease vaccine responsiveness. Several studies have shown that mycophenolate mofetil (MMF) [34, 67, 68] and sirolimus [69, 70] reduce the immunogenicity of influenza vaccine. Although both drugs are classical "antiproliferative" immunosuppressive drugs, their modes of action differ in terms of how they modify signaling pathways and the resulting phenotypes [71]. MMF causes a dose-dependent reduction in proliferation of stimulated B-cells [72]. MMF has been shown to inhibit B-cell activation and proliferation and plasma cell formation [35, 73•]. In addition, MMF preferentially reduces virus-induced Th2 cytokine expression, relative to that of Th1 cytokines [74]. Aside from these recent findings, the effect of most immunosuppressive drugs on vaccine responses remains unknown.

Current Strategies to Improve Vaccine Responses in Transplant Recipients

The marked impairment in vaccine responses in SOT cohorts is akin to the experience in the vaccination of individuals over the age of 65 against influenza and *Streptococcus pneumoniae*. Antibody titers were lower, and there was little protection afforded from pneumonic illness [75-77].

In efforts to overcome poor vaccine immunogenicity, various strategies have been proposed or attempted in immunocompromised groups with divergent outcomes.

1. Higher antigen load: Providing a higher dose of influenza antigen per vaccination or the use of booster doses is believed to lead to increased follicular dendritic cells loaded with antigen in lymph nodes capable of prolonging

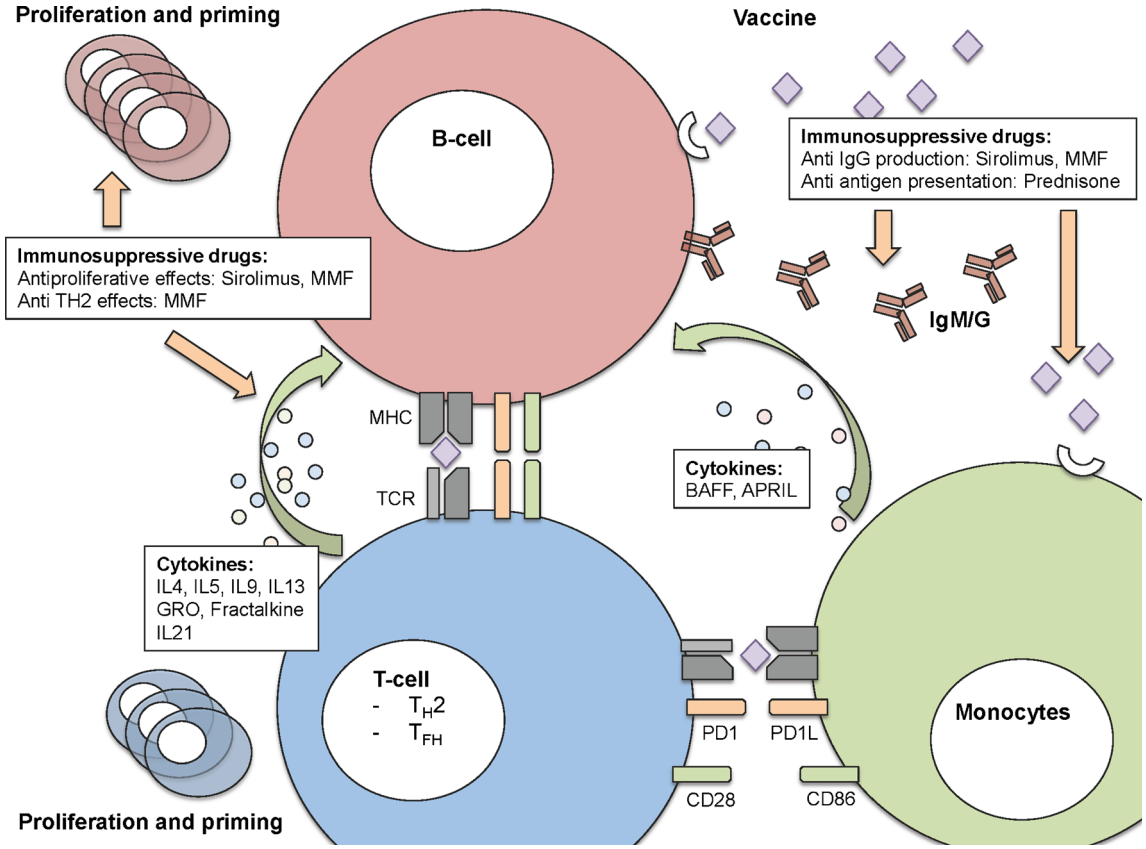

Fig. 1 Interaction of vaccine-stimulated immune cells in the context of transplantation. Virus-specific B-cells receive important growth factors and cytokines from T-cells and monocytes. In response, antigen presentation is increased in a feedback loop. The activation of T-cells is strongly modulated by co-stimulatory signals (such as CD28/CD86 or PD1L/PD1) and immunosuppressive drugs

B-cell stimulation. Results from such strategies have been mixed and in an HIV cohort, Cooper et al. investigated the use of a higher influenza antigen load, but this did not significantly alter the rates of seroprotection [78]. Similarly, high-dose vaccine in an SOT cohort did not achieve higher seroconversion [51]. In an elderly population, however, high-dose vaccine did, in fact, increase seroconversion rates [79].

2. Altered route of administration: Theoretically, intradermal vaccination carries benefits of improved immunogenicity via direct and enhanced stimulation of Langerhans cells and the subsequent priming of cell-mediated and humoral immune responses. Again, in a recent randomized controlled trial, Baluch et al. found no significant difference in influenza seroconversion rates comparing high-dose intradermal with standard intramuscular vaccination in a cohort of SOT recipients [53].
3. Use of adjuvants: Adjuvants are widely employed in vaccination, acting to nonspecifically stimulate the local innate immune response, thus heightening ultimate humoral responses [33]. Aluminium salts and squalene-based oil-in-water emulsions are the two primary agents in general use. They promote increased cellular trafficking, with improved antigen uptake and presentation [33]. Surveillance of the adjuvanted pandemic H1N1 vaccines demonstrated improved rates of seroconversion even in the immunocompromised. Dhedin et al. more recently reported humoral responses with an adjuvanted influenza vaccine equivalent to that observed in natural infection [80]. In contrast, Manuel et al. reported that despite adjuvants and a double-dosage regimen, humoral responses remain significantly impaired in SOT recipients [81]. Novel adjuvants such as TLR agonists are emerging as a means to even more specifically and potently stimulate the host immune response. Concerns arise, however, in relation to this potency, with potential consequences of overstimulation of innate responses leading to poor tolerability and high rates of adverse reactions. Specific to SOT recipients, it has been proposed that the use of potent adjuvants can give rise to the generation of allo-antibody and result in an increased risk of allograft rejection [82]. To date, such concerns regarding rejection have not been substantiated [83, 84]; thus, adjuvanted vaccines, particularly in those with impaired host responses, represent a valid means by which to advance vaccination. Even more attractive is the ability to specifically boost the immune component often lacking in cohorts such as SOT recipients or the elderly. A means for tailoring host responses to

favor Th2-mediated stimulation of B-cells stands to specifically overcome the deficits identified in such hosts: an impairment of the extent and diversity of proliferative adaptive responses [75].

"Next-Generation" Strategies to Improve Vaccine Responses in Transplant Recipients

Novel Types of Vaccines and Adjuvants

A number of innovative technological advances are being applied to vaccination to improve existing vaccines and to develop new vaccines against existing and emerging pathogens. Recently, vaccines using recombinant protein technology and containing highly conserved regions of influenza A virus have demonstrated immunogenicity and cross-reactive potential, offering an option to move away from annual influenza vaccination and provide cross protection against novel assortments [85, 86]. One such vaccine, however, was highly dependent on the use of an adjuvant in the form of flagellin, a Toll-like receptor (TLR)-5 agonist, to generate sufficient immunogenicity [85].

Other novel technologies include the use of nanoparticles [87], vector-based vaccines, and nucleic acid vaccines [88, 89]. Theoretically, these systems can deliver prolonged antigen release and multiple antigens, perhaps a situation more akin to that occurring during natural infection. To date, however, challenges continue to exist in the form of stability, cytotoxicity, and durable immunogenicity, as demonstrated by the need for a potent adjuvant in the influenza vaccine example above. Likewise, DNA vaccines are limited, due to the requirement for multiple administrations, and vector-based approaches, due to the development of host immunity targeting the vector [88].

In addition to redesigned vaccines, novel types of adjuvants selectively targeting specific immune signaling cascades may be used for high-risk patient cohorts. Although TLR-agonists may be potent inducers of Th1 immune responses, for antibody-based vaccines, this may not be the right strategy [33]. Safety issues in terms of triggering rejection episodes have to be carefully assessed and explored in all novel adjuvant approaches. Temporally triggering Th2 immune responses could conceivably induce a more specific B-cell and antibody response—which may, for example, be safer in transplant recipients.

Personalizing Vaccination with Genetic Risk Profiling

The identification of single nucleotide polymorphisms (SNPs) associated with postvaccine phenotypes carries potential for application to the individualization of vaccination strategies. To date, no genome-wide association studies (GWASs) addressing vaccination have been performed in transplant recipients. To the best of our knowledge, GWASs have been conducted focusing only on anthrax [90], small pox [23, 91, 92], HIV [93], and Hepatitis B virus [94]. However, these studies were relatively small, and vaccine failure for these vaccines in an otherwise healthy population is often low. Therefore, these studies might have been underpowered. One GWAS explored the association of SNPs with side effects from vaccines [95].

A more focused study addressing a number of innate immune-associated genes has been undertaken with respect to measles vaccination. In immunocompentent children, 12 antiviral genes from innate signaling cascades (of 307 evaluated genes, including, among others, RIG-I, Interferon-induced GTP-binding protein Mx1 [Mx1], 2'-5'-oligoadenylate synthetase 1 [OAS1]) showed genetic variants, which were associated with measles-specific antibody titer variations [96•, 97]. In particular, SNPs in the Interferon-λ signaling cascade (IFNL3) were associated with twofold higher postvaccine titers [96•]. Polymorphisms in the region encoding this most recently identified Interferon family have been strongly associated with host responses to hepatitis C virus [98-100]. Emerging data implicate IFN-λ as an innate cytokine modulating the balance in helper T-cell responses; thus, such SNPs can have important influences on vaccine responses [101-103]. In the near future, patients identified as carrying "risk" polymorphisms could be vaccinated with different protocols, with increased dosages, different application routes, or vaccines containing adjuvants that may compensate for a specific immune defect in a more safe and targeted manner.

Stratifying Host Factors to Individualize Vaccine Strategies in Transplant Recipients Using Computational Modeling

As was previously discussed, vaccine responses in transplant recipients will vary due to multiple host-, vaccine-, and transplant-related factors (Fig. 2). It is clear from the body of evidence available that the strength and quality of the response to vaccination is a composite of the quality of antigen (immunogenicity, broadly conserved epitopes) used to emulate the pathogen and the integrity of the host response. The host factors involved during a vaccine response include all aspects of "–omics," such as genomics, proteomics, and metabolomics [104•, 105-107]. The resulting host-dependent immune reactions are driven by the highly complex spatio-temporal interplay between signaling pathways, cells, and tissues—a prime target for systems biology modeling approaches.

Computationally modelling the dynamic response of the immune system is a challenging task even without taking host

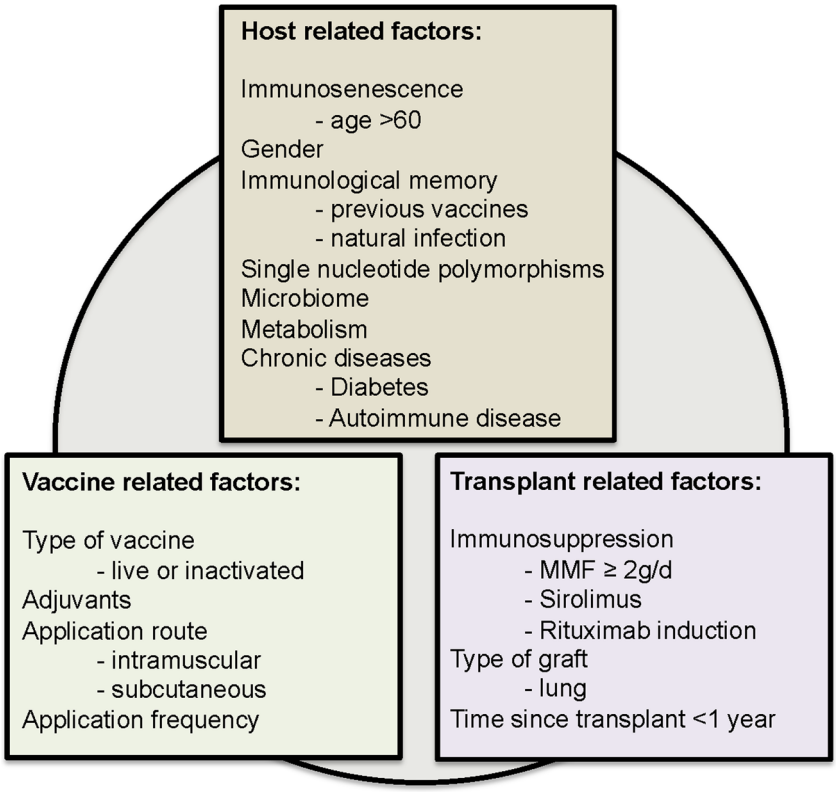

Fig. 2 Factors modulating vaccine-stimulated immune responses. These factors should be implemented into computational models for clinical usages

variability into account. Mathematical models that focus on cell-to-cell interactions in the immune system range from highly abstracted representations of immune and target cells [108] to more detailed ones that, for example, distinguish between B- and T-cells [109]. However, most of these models represent the system rather at the level of phenomenological interactions between subpopulations of immune cells, and not mechanistically. This holds also for the most advanced models in which various immune cell subpopulations are integrated on the basis of previous models [110]. Overall, as was shown recently by a comparative study of mathematical models describing immune responses to influenza infection, the predictive ability of different, state-of-the-art immunological models is rather limited; it appears that the system behaviors captured are largely dictated by the data sets used for model calibration, with additional biases because human experimental data are scarce [111].

In contrast to the models outlined above, systems biology models were developed primarily to understand molecular mechanisms in single signaling pathways of importance to the immune system. These approaches allowed for detailed insight into, for example, T-cell receptor signaling and the mechanistic foundations of T-cell memory [112••]. In other cellular contexts, for example, detailed mechanistic models have been developed to capture the dynamics of interferon signaling from the receptor to target genes such as antiviral genes. Model-based analyses of molecular signaling mechanisms have been published for type I [113•, 114] and II [115], but not yet for type III Interferons. In principle, such molecular-level computational models based on in vitro or in vivo data allow manipulation of variables of interest (e.g., genomic variation) and the determination of downstream effects [112••, 116, 117].

In transplant recipients, examples of such variables of interest for simulation-based analysis of factor influences are given in time since transplantation, allograft type, and immunosuppressive treatments (dose and serum peak/trough levels). The effects introduced by exogenous immunosuppression are particularly influential in SOT recipients, where initial intensive immunosuppression—which is then maintained at a basal level—strongly impacts immune response in general and vaccine responsiveness in particular (Fig. 3). In order to extend quantitative models of an immune response to transplant recipients, the mechanisms and extent of immunosuppression have to be quantified accurately; such studies do not exist to date.

The innate immune response is the first step of the signal cascade and likely assumes even more importance in SOT recipients with regard to triggering downstream priming of T- and B-cells [118-120]. Therefore, to explore variable outcomes (for example, seroprotection or seroconversion) prior to vaccination using clinical or immunological parameters, systems biology and immunology models need to be ultimately integrated into multilevel frameworks as used in oncology

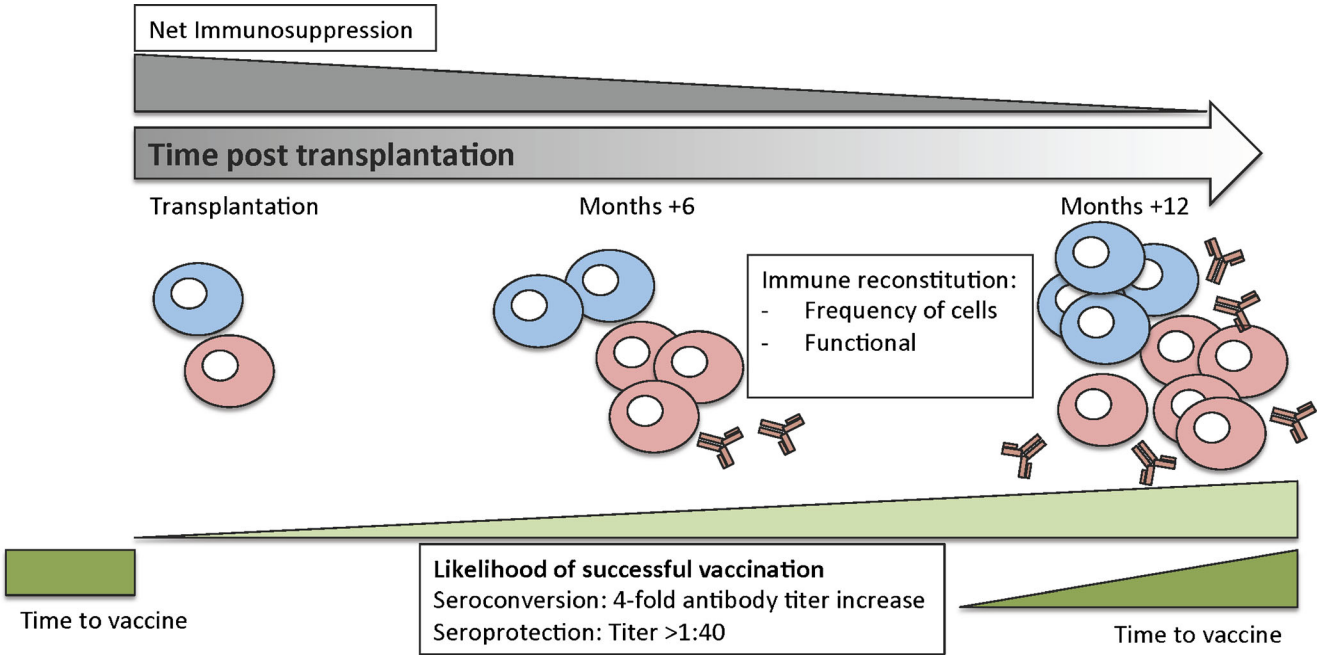

Fig. 3 Dynamic changes of vaccine response. The response rate toward a vaccine is highly dependent on the time posttransplant, frequency of immune cells, and immunosuppressive drugs

[121]. Only the integration of population-level and mechanistic models will allow linkage of genotypes such as SNPs in specific signaling pathways with clinical outcomes in a predictive manner.

Finally, computational immunology has barely addressed the problem of systematic estimations of interindividual variability from in vivo, clinical data, because many fundamental studies were carried out in vitro. However, such analysis is required to generate patient-specific predictions. In related fields such as pharmacokinetics, the standard methodological approach is to employ nonlinear mixed effect models—that is, models that capture common mechanisms (fixed effects) as well as variability between individuals (or subgroups of the population; so-called random effects) [122]. Calibrating these type of models to experimental in vitro or clinical data, however, faces important computational challenges and usually requires small-scale models [123]. This currently hampers progress toward the ideal of patient-specific vaccine optimization using purely computational predictions. Despite these important considerations, prediction of vaccine responses based on system-wide measures is achievable, but challenges remain for robust population-wide predictions based only on prevaccination measures, especially in partially efficacious vaccines such as that for influenza. In the future, further research in this fast evolving field is required to extract the maximum potential from these technological advances providing a unique insight into determinants of protection and selecting out individuals for a tailored vaccine schedule or to identify key immunologic cascades for targeted adjuvants.

Summary and Outlook

The field of vaccination is highly active and substantiates the medical profession mandate to strive for disease prevention. In that regard, efforts should be directed to those most at risk—namely, immunocompromised individuals. Many novel advances are entering into clinical trial stages, and these provide hope for both an improved and a broader spectrum of vaccine options in the future. While delivery methods remain vitally important, the host response to vaccination is a critical determinant of outcome. In particular in relation to immunocompromised hosts, a window exists to vaccinate early in the clinical care pathway to optimize the chance of success. However, the efficacy of annual influenza vaccination in heavily immunocompromised hosts draws the challenges into sharp focus. Until a "universal influenza vaccine" is realized in clinical practice, it is imperative that we devise strategies to boost response to existing vaccines by individualizing vaccine schedules or using existing or new adjuvants. Allied to this is further research into the immune cascades determining vaccine efficacy, taking advantage of systems biology and mathematical modeling approaches that could ultimately enable individualized vaccination strategies to optimally protect the most vulnerable hosts against disease.

Compliance with Ethics Guidelines

Conflict of Interest Daire O'Shea declares no conflicts of interest. Joerg Stelling has a grant pending from the Swiss National Science Foundation. Lukas A. Widmer declares no conflicts of interest. Adrian

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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