HHS Public Access

Author manuscript

Expert Rev Vaccines. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Expert Rev Vaccines. 2019 January ; 18(1): 75–87. doi:10.1080/14760584.2019.1559063.

Current perspectives in assessing humoral immunity after measles vaccination

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Abstract

Introduction.—Repeated measles outbreaks in countries with relatively high vaccine coverage are mainly due to failure to vaccinate and importation; however, cases in immunized individuals exist and raise questions about suboptimal measles vaccine-induced humoral immunity and/or waning immunity in a low measles-exposure environment.

Areas covered.—The plaque reduction neutralization measurement of functional measles-specific antibodies correlates with protection is the gold standard in measles serology, but it does not assess cellular-immune or other parameters that may be associated with durable and/or protective immunity after vaccination. Additional correlates of protection and long-term immunity and new determinants/signatures of vaccine responsiveness such as specific *CD46* and *IFI44L* genetic variants associated with neutralizing antibody titers after measles vaccination, are under investigation. Current and future systems biology studies, coupled with new technology/assays and analytical approaches, will lead to an increasingly sophisticated understanding of measles vaccine-induced humoral immunity and will identify “signatures” of protective and durable immune responses.

Expert Commentary.—This will translate into the development of highly predictive assays of measles vaccine efficacy, effectiveness, and durability for prospective identification of potential low/non-responders and susceptible individuals who require additional vaccine doses. Such new advances may drive insights into the development of new/improved vaccine formulations and delivery systems.

Keywords

Measles; Measles Vaccine; Measles-Mumps-Rubella Vaccine; Genetic Association Sudies; Genetic Variation; Gene Polymorphisms; Gene Expression; Systems Biology; Antibody; Immunity; Humoral; Immunity

Disclosure of whether any or part of the data have been previously published

Figure 1 in this review has been previously published (Hum Genet. 2017;136:421-435, PMID: 28289848) [126, 127] and is used with permission from *Human Genetics*.

1. Measles in high vaccine coverage settings and measles vaccine failure.

Measles is a highly contagious disease, which has been eliminated in the United States for more than **18** years. It is still a common threat in the underdeveloped world with potentially life-threatening sequelae and over 450 known pediatric deaths each day [1]. It was estimated that over 7 million people were infected with measles worldwide in 2016 with 89,780 reported measles-related deaths [2]. Measles outbreaks have been limited in the United States during the last few years and are mainly a result of importation and predominantly involve unvaccinated individuals who travel, as well as their contacts (e.g., 86 reported measles cases in 2016; 118 measles cases in 2017; and 124 measles cases from 22 states in 2018, as of August 11, 2018) [3, 4]. In 2017, the World Health Organization announced a four-fold rise in the number of measles cases in Europe (23,927 cases), with large outbreaks affecting more than 15 European countries [5, 6]. Furthermore, over 41,000 measles cases were reported in Europe for the first half of 2018 (the most affected countries were France, Georgia, Greece, Italy, the Russian Federation, Serbia, and Ukraine), with at least 37 reported pediatric deaths [5, 6]. This resurgence of measles is primarily due to failure to vaccinate and sustain high immunization coverage with the two-dose measles vaccination schedule in the affected countries/regions. However, this is an indication that measles is and will continue to be a public health concern for both developing and developed countries for the foreseeable future.

Long-term sequelae of measles are more serious and common than previously thought. A recent study assessing national-level information from England, Wales, the United States, and Denmark, from both the pre- and the post-vaccine era, provided statistical/modeling evidence for the association of measles with the long-term increase (approximately 2- to 3-year observed impact) of non-measles infectious disease mortality in children [7]. These non-specific effects of measles on immunity to other pathogens are likely due to measles-induced immunosuppression from lymphocyte depletion of memory B and T lymphocytes and/or from measles-related functional immune impairment [8–11] . Recent research also re-estimates the rate of developing subacute sclerosing panencephalitis/SSPE, a fatal progressive inflammation of the brain resulting from persistent measles virus (MV) infection, to be 1 in 609 after measles disease occurring in infancy [12].

To prevent persisting measles endemicity and target measles for global eradication, achieving and sustaining herd immunity of at least 90–95% is required [13–17]. It is generally accepted that the live attenuated measles vaccine has a high protective efficacy, particularly after two vaccine doses (although it may be lower and not life-long compared to the wild type virus infection), and a field effectiveness of 94.1% (IQR, 88.3%-98.3%) after two doses [18]. Accordingly, measles mainly affects unvaccinated individuals. It is also indisputable that a two-dose measles vaccination program must be implemented and sustained globally to reduce measles morbidity/mortality and achieve measles eradication. What is still a subject of debate is the ability of the current measles vaccine to sustain long-term protective immunity and adequate herd immunity in settings with no wild type virus exposure (i.e., no boosting of immunity resulting from asymptomatic infection).

Primary measles vaccine failure (a failure to develop protective immunity after vaccination) is not uncommon (approximately 2 – 12% for children immunized at/around one year of age [19–21]) and can be partly managed by the administration of a second dose of vaccine and by increasing the age at first vaccination (in regions with low measles incidence) to ensure immune system maturity and loss of maternally-acquired antibodies [22]. The assessment of secondary vaccine failure (waning immunity or failure to sustain protective immunity over time) can be difficult and requires long-term monitoring of measles vaccine-induced adaptive immunity after the first and second vaccine doses and ideally vaccine efficacy data, immunogenicity data and epidemiological information on measles cases/outbreaks in the geographical area.

Annual measles outbreaks in high vaccine coverage settings also continues to occur. Although these outbreaks typically involve importation and mostly affect unvaccinated individuals, they also reveal surprisingly high numbers of vaccine failure among one- and two-dose recipients of measles-containing vaccine who were infected [15–17, 22–53]. In a recently published study of registered laboratory-confirmed measles cases in California between 2000 and 2015, Cherry and Zahn [51] report 232 measles cases with a documented vaccine history, of which 9% (20 cases) were after one dose and 11% (26 cases) were after two doses of measles-containing vaccine (median 16.7 years after last vaccination, range 6 to 23.6 years after last vaccination), indicating the likely occurrence of waning immunity [51]. Earlier studies suggest a secondary measles vaccine failure rate of ~5%, approximately 10–15 years after the second immunization [31, 54]. Previous studies have also reported a combination of laboratory methods (measles plaque reduction neutralization assay [PRN], measles IgG avidity assays, and detection of MV RNA by RT-qPCR) and criteria for classification of measles reinfection cases and secondary vaccine failure [55, 56]. Larger and more sophisticated studies are still needed to more precisely estimate secondary vaccine failure rates (waning immunity) in low measles incidence (high vaccine coverage) settings.

2. Immune measures and correlates of protection after measles vaccination.

Measles virus cell entry and infection is mediated by the known MV-specific cellular receptors SLAM/CD 150, nectin-4/NECTIN4/PVRL4 and CD46 (operational only for attenuated MV strains) [57–60]. Wild type and attenuated measles viruses elicit differential innate/inflammatory immune responses (NFκB signaling/activation of the NLRP3 inflammasome with no detectable interferon type 1 response for the wild type MV strains and detectable induction of interferon-stimulated genes [ISGs] for the attenuated MV strains, respectively), but the implications of these differences for the development of adaptive immunity are unclear [61–63]. Protective immunity to measles is accomplished by high-avidity neutralizing antibodies directed to the MV surface glycoproteins, primarily the hemagglutinin/H protein (with a modest contribution of antibodies to the fusion/F protein), which effectively neutralize SLAM-using wild type MV infection of lymphocytes [54, 61, 64–67]. Measles vaccine elicits both neutralizing and non-neutralizing antibodies against different MV proteins, as well as measles-specific cellular immunity, with limited correlation between measures of the humoral and cellular arms of immunity [68]. $CD4^+$ T

cells are not essential, but they (in particular, the follicular T-helper/Tfh cells in the lymph nodes) can facilitate protective humoral immunity by providing help for the formation of germinal centers, for the activation and differentiation of B cells, and for isotype switching and affinity maturation in antibody-secreting cells/ASCs [69]. $CD8^+$ T cells are considered important for viral clearance [61]. Functional measles-specific neutralizing antibodies after vaccination (anti-H and anti-F) are quantified using a classical plaque reduction neutralization test (PRN) or its improved automated version, the plaque reduction microneutralization (PRMN) assay,[70–72] in specialized laboratory settings by trained personnel. Routinely, these assays rely on CD46-mediated *in vitro* infection of Vero cells (that do not express human SLAM) with attenuated Edmonston-based MV strains; and for these reasons, the results may not fully reflect the protective antibody efficacy upon wild virus measles exposure [54, 73].

With the above taken into consideration, the currently accepted correlate of protection against measles is a PRN titer of MV-specific neutralizing antibodies >120 (or >120 mIU/mL), which predicts protection from clinical disease [64, 71, 72, 74]. It has been repeatedly shown that serum antibodies (e.g., passively transferred immunoglobulins or transplacentally acquired antibodies) are sufficient to confer protection from measles [54, 61, 64–67]. However, it has been demonstrated that subjects with low/undetectable PRN antibody levels may still be protected from clinical measles, suggesting a role for cellular immunity in protection [54, 61, 64–67]. In addition to the PRN assay, seroprevalence studies assessing measles vaccine-induced humoral immunity apply an array of other assays (reviewed in [75–81], including a variety of automated commercial immunoassays (e.g., multiplex microsphere/bead fluorescence-based immunoassays) and microtiter-plate enzyme-linked immunoassays (EIA) reporting qualitative and/or quantitative results. Among the most commonly used are the Enzygnost® Anti-Measles Virus/IgG EIA (Siemens Health Care Diagnostics GmbH, Marburg, Germany) and the Serion Measles IgG EIA (Institut Virion \Serion GmbH, Würzburg, Germany) [75]. With few exceptions (the Enzygnost® Anti-Measles Virus/IgG), these assays were not calibrated against the 2nd WHO international measles standard (the 3rd WHO international measles standard is not currently recommended for EIA calibration[82]). More importantly, EIA assays measure antibodies to other abundant MV proteins (e.g., the N protein in addition to H and F) and have limited ability to measure antibodies to conformational epitopes; thus, their utility for categorization of individuals into immune or non-immune and assessing potential measles susceptibility is limited, particularly at the lower range of antibody titer [75]. A recently developed measles-specific assay using proteome microarray (antibody array) technology successfully detected antibodies against five MV proteins (H, F, N, P and L) in recipients of measles vaccine, and the measures/patterns were well correlated with the neutralizing antibody response [83].

Antibody avidity assays are also emerging as useful tests for distinguishing primary from secondary humoral immune response during measles outbreaks in high vaccine coverage settings. Avidity is defined as the cumulative strength of attachment/binding of multivalent antibodies to multivalent antigens. A new MV-specific IgG avidity assay was developed by the CDC using a modified commercial EIA assay with the use of the denaturant diethylamine (DEA), and validated with a panel of reference serum samples [84]. This assay provides useful thresholds for classification of antibodies into high/low or intermediate

avidity and can supplement IgM antibody assays in the serological assessment of measles cases, as well as facilitate the classification of secondary vaccine failures [84].

Measurement of other markers of measles-specific humoral immunity are also currently being introduced and used, but their outputs (immune outcomes) are not generally accepted as correlates or surrogates of protection against measles. The memory B cell ELISPOT assay uses peripheral blood mononuclear cells (PBMCs) or purified B cells to provide a quantitative measure of the frequencies of pre-existing measles-specific memory B cells after non-specific polyclonal B cell stimulation followed by enumeration of antigen-specific ASCs [85–89]. Similarly, a plasmablast ELISPOT assay (without non-specific B cell stimulation) directly measures the frequencies of the antigen-specific circulating plasmablasts that peak around day 7 after vaccination [90]. There has been some controversy in the literature over the correlation of measles-specific antibody titers with the frequencies of measles-specific memory B cells and the use of the latter as a predictor of the duration of antibody response/antibody waning [87–89]. Memory B cells are important for a prompt humoral response upon antigen re-exposure, but most likely long-term measles-specific antibody production is maintained by antigen-specific long-lived plasma cells in the bone marrow rather than reactivation/differentiation of memory B cells [91–95]. No feasible assay for large-scale studies exists today to reliably measure the quantity and characteristics of antigen-specific long-lived plasma cells (as well as the antigen-specific Tfh cells) in humans due to their specific niche/homing (ideally assessment requires bone marrow and lymph node biopsies). Assessment of measles vaccine-induced humoral immunity in vulnerable populations (particularly in pediatric patients suffering from chronic infections and/or immunosuppression) is also important for the maintenance of measles control and eradication/elimination efforts for the general population. A study assessing B cell compartment immunity in 70 HIV-1-infected children established the importance of early antiretroviral therapy for the maintenance of long-term immunity (measles-specific memory B cell frequencies and protective measles antibody titers) after routine vaccinations [96]. Similarly, other conditions associated with immunosuppression (e.g., transplantation and primary immunodeficiencies) often lead to impaired development and/or waning of measles vaccine-induced immunity [97–99]. Monitoring of measles immunity in such cases is critical for the optimization of population vaccination strategies and maintenance of long-term protection against measles. Addressing the current knowledge and public health gap, as well as barriers to measles elimination activities, requires new approaches in assessing and predicting humoral immune response after measles vaccination in order to prospectively identify vaccine responders and non- or low-responders and/or potentially measles susceptible individuals whose protective titers wane over time. Such approaches and perspectives are in line with the WHO 2012–2020 Global Measles and Rubella Strategic Elimination Plan and the Midterm Review which recommended “research on susceptibility profiles for measles, and research related to outbreaks in high vaccine coverage settings [100], and are reviewed in the sections below with a focus on identifying determinants/ signatures of measles vaccine-induced humoral immunity.

3. Contribution of HLA and candidate immune response genes to measles vaccine-induced variations in humoral immunity.

Over the last 23 years, our group has investigated the wide inter-individual variation in circulating humoral antibody responses after routine measles vaccination in highly immunized healthy populations and has systematically defined genetic contributions to inter-individual immune response variations and vaccine failure (reviewed in [17, 49]).

Both host genetics and environmental factors contribute to variability in immune responses to vaccines. Among the host genetic determinants that are involved in protective immunity against measles are the highly polymorphic HLA and non-HLA genetic variants. In this regard, HLA allelic associations with humoral immune responses after measles vaccination have been studied in detail. Measles vaccine-induced immunity can involve strong HLA class I- and class II-restricted CD8+ and CD4+ T cell immune responses. Some key HLA class I (B*57:01, B*35:03) and class II (DQB1*06:02, DQB1*03:03, DB1*07:01 and DRB1:15:01) alleles have also shown confirmed associations with inter-individual variations in measles antibody responses after two doses of measles vaccine [101]. Furthermore, in a large cohort of 2,506 healthy immunized subjects (age 11 to 41 years), specific class I and class II HLA types—such as B*57:01, DQB1*06:02, and DRB1*15:05—have been clearly associated with measles vaccine-specific neutralizing antibody titers [102]. These reproducible associations between HLA molecules and immune response outcomes have led to the identification of measles virus epitopes presented by HLA [103–105]. Such synthetic peptides/epitopes can be used to design personalized measles vaccines [106, 107].

Multiple population-based vaccine studies have also demonstrated associations between candidate genes/SNPs and variations in measles vaccine-induced immune responses, including vaccine non-response and vaccine failure [17, 26, 101, 106, 108–124]. One study included healthy children (n=745) who received 2 doses of measles vaccine and were genotyped for a panel of innate SNP markers, such as vitamin A (RARA, RARB, and RARG), and vitamin D receptor (RXRA) genes, a transmembrane receptor CD46, CD209 (DC-SIGN), host antiviral sensor and effector (VISA, DDX58, OAS1-3, MX2, ADAR), TRIM (TRIM 5, 22, 25) and TLR (TLR2,3,4,7,8) genes. Multiple polymorphisms and haplotypes in these genes have been found to be significantly associated with humoral and/or cellular immune response markers [109, 112–114, 125], and some were subsequently replicated (e.g., the *CD46* rs2724384 genetic variant [126, 127]). These findings point to additional non-HLA genetic variants/genes as being critical determinants modulating the adaptive immune responses to measles vaccine. Likewise, multigenic effects on measles vaccine-induced immunity have been examined using a large collection of SNPs (n=1,912) that tag 126 candidate genes. Combined analyses of all these SNPs provided evidence that a multigenic model may explain variations in antibody levels (p=0.05) and in cell-mediated IFN-g ELISPOT response (p=0.02) variance [110]. The genetic studies reported above have identified important and informative genetic determinants of measles vaccine response heterogeneity and led to a large-scale state-of-the-art genome-wide association study (GWAS) that allowed for identification of additional genetic determinants (SNPs and immune response pathways) of measles vaccine-induced immunity [126, 128].

4. Genome-wide genetic association studies and measles vaccination: from genetic association to function of genetic determinants of humoral immunity.

The advances in technology and statistical analysis during the last decade have allowed for enhanced genome-wide interrogation of the human genome (i.e., GWAS studies) for identification of determinants of host response to measles vaccination in an unbiased (by prior knowledge) way [126, 129–131].

In a sophisticated GWAS in children, Feenstra et al. [129] identified two genetic loci on chromosome 1 that were associated with febrile seizures after measles-mumps-rubella (MMR) vaccination but not with unrelated febrile seizures. These two genetic loci harbor the interferon-stimulated gene *IFI44L* and the measles virus receptor gene (for attenuated MV strains) *CD46.*

In a population-based study of 2,872 healthy subjects (age 11–41 years) who had received 2 doses of MMR vaccine, we performed measles neutralizing antibody titer assays after a second vaccination (median 3.4 years). After correcting for multiple confounding variables (e.g., age, time since last MMR vaccination, etc.) and excluding subjects with conditions affecting immune response, we documented a wide range of MV-specific humoral immunity, with a median Ab titer of 845 mIU/mL (IQR: 394 to 1,683). Among these subjects, 94 subjects (3.3%) had non-protective levels of circulating neutralizing antibody (<120 mIU/mL), and 338 subjects (11.8%) had neutralizing antibody <210 mIU/mL, which corresponds to a PRN neutralizing dose/ND_{50} titer of 120 [132]. These data and other recent reports from the literature [22, 51, 52, 133] raise questions about suboptimal measles vaccine-induced humoral immunity and/or waning immunity among highly vaccinated populations in a low measles exposure environment.

The above cohort was used to assess for genetic factors contributing to MV-specific neutralizing antibody response in the first GWAS study of measles vaccine-induced immunity, which estimated the heritability of vaccine-induced measles antibody titers to be ~49% [126, 127]. This GWAS (unrelated to the GWAS by Feenstra B. et al., on febrile seizures [129]) independently identified the two chromosome 1 genetic regions (the 1q31.1 region harboring the *IFI44L* gene with 9 significant SNPs; and the 1q32 region harboring the *CD46* gene with 20 significant non-coding SNPs) to be associated with the measured MV-specific neutralizing antibody titer after MMR vaccination. Several overlapping SNP associations were found between the two studies (i.e., the intergenic SNP rs1318653 near the *CD46* locus and the coding *IFI44L* His73Arg SNP 273259) in concert with multiple SNP associations with immune responses not reported previously [126]. The top SNP association in subjects of European ancestry is an intronic genetic variant rs2724374 (p-value = 4.88×10^{-09}), located near the *CD46* intron 8-exon 8 boundary, which is demonstrated to affect/cause genetic splicing (the skipping of the *CD46* serine/threonine/proline-rich/STP B exon), resulting in differential abundance of CD46 isoforms associated with different genotypes [126, 134, 135]. The minor allele of this SNP (G) was significantly associated in a dose-response dependent manner with ~50% reduction in MV neutralizing antibody titer

after vaccination [126]. This allele is likely responsible for the splicing of exon B to favor the generation of CD46 isoforms with a shorter (and less O-glycosylated) STP region, as demonstrated by a genotype-specific RT-PCR isoform analysis and a DEXSeq analysis of NGS data [126]. We and others have suggested that MV binding and fusion capacity in cells expressing the *CD46* C1/C2 (shorter) isoforms vs. the BC1/BC2 (longer) isoforms differ, and this variance may translate to differences in both viral replication and triggering of immune response pathways after live virus vaccination [126, 136–138]. The functional effects of the *CD46* rs2724374 genetic variant are summarized in Fig. 1. Ongoing functional studies in human cells expressing/overexpressing different CD46 isoforms demonstrate clear difference in MV infection/replication and innate immune pathway activation depending on the prevalence of specific CD46 isoforms (*Haralambieva and Poland*, unpublished data). Lastly, the presence/absence of STP exons (associated also with difference in the O-glycosylation) in the extracellular portion of CD46 can result in altered processing, altered CD46 shedding/cleavage by metalloproteinases, altered downregulation and cell surface expression, and profound differences in T cell function and TCR signaling [139, 140].

The discovery of *CD46* and *IFI44L* genetic variants as determinants of measles vaccine-induced humoral immunity (and adverse events) after measles vaccination could translate into the development of inexpensive chips/platforms for prospective identification of potential non-responders and susceptible individuals who will eventually need additional vaccine doses, as well as improved vaccines capable of overcoming any genetic restrictions.

5. Statistical challenges and solutions for analyzing high-dimensional data (genetic association studies, GWAS).

It is well known that immune response is strongly influenced by both genetic and environmental factors. Because the immune system is fine-tuned [141], individual genetic factors tend to have small effects on immune response, making it statistically challenging to uncover the main causes. To overcome this challenge, careful study design and large sample sizes are crucial. The design of studies should control for factors known to influence response, such as age at immunization, sex, prior vaccinations, etc. It is also critical to control for laboratory batch effects of assay measurements, and to normalize response to make unbiased comparisons [142]. Although there are multiple genes known to influence immune response, such as genes in the HLA region, the agnostic approach of GWAS offer the advantage of new discoveries, albeit at the requirement of large sample sizes.

GWAS studies [143] have achieved enormous success at identifying the genomic regions that harbor genetic determinants of complex traits [144–150], with over 2,000 traits registered in the Catalog of published genome-wide association studies with association *p*-values less than 10^{-5} with single nucleotide polymorphisms [151]. This tremendous success can be attributed to the large sample sizes required to have sufficient power to detect small effects of genes, as well as inexpensive genotyping microarrays that contain a large number of SNPs. Furthermore, large-scale reference panels provide a way to reliably impute SNPs that are close to the SNPs that are measured in microarrays [152], resulting in approximately 10 million SNPs frequently available for analyses.

To summarize GWAS *p*-values that measure the marginal association of one SNP at a time with a trait, Manhattan plots of *p*-values are frequently used, followed with LocusZoom plots for regions of interest [153]. This provides a way to focus on the SNPs with the smallest (i.e., most significant) *p*-values in distinct regions. The SNPs with the smallest *p*-values are sometimes called the lead or index SNPs. Because there are many SNPs tested for their association with a trait, GWAS results are most reliable when SNP associations achieve the accepted genome-wide statistical significance threshold of $p\text{-value}<5\times10^{-8}$ [154, 155].

A caution about the lead SNP is that there is a reasonable chance that it does not have a direct causal effect on the trait [156]. Rather, the lead SNP is often in linkage disequilibrium/LD with an unmeasured causal variant [157]. This is because the SNPs on microarrays, called tag-SNPs, are chosen because they serve as surrogates for large genomic regions. Their ability to be faithful surrogates stems from their high correlation with neighboring unmeasured SNPs (i.e., high LD) [158, 159]. This means that the association between a tag-SNP and a trait can be indirect, resulting from a tag-SNP statistically associated with an unmeasured causal SNP and the causal SNP having a direct effect on the trait. To increase the density of SNPs, hopefully capturing the causal variant or at least refining its location, statistical imputation of neighboring SNPs is a widely accepted technique [160, 161].

The patterns of LD among SNPs can be complex. This makes it challenging to determine the underlying causal variants by inspecting the marginal association of a trait with one SNP at a time. Statistical methods that jointly analyze all the SNPs in a region, particularly methods that are designed for fine-mapping [162, 163], are useful to prioritize SNPs for subsequent functional studies. Additional insights can be gained by genomic annotation of SNPs that assign biological function based on publicly available resources [164–168].

Many of the trait-associated SNPs discovered by GWAS are not in gene-coding regions; rather, they map to non-coding regions, often in areas enriched for regulatory elements, such as enhancers, promoters, insulators, and silencers [169]. This suggests that SNPs discovered by GWAS influence the amount of expression of nearby genes (referred to as expression quantitative trait loci; eQTL), and this altered expression ultimately influences the trait. Statistical methods can be useful to integrate eQTL data (i.e., genes whose RNA levels are associated with specific SNPs) with GWAS data (i.e., traits associated with specific SNPs) in order to quantify the evidence of a causal pathway from SNP to gene-expression to a complex trait. Some methods are based on testing causal models [170], some are based on Mendelian randomization [171], and some are Bayesian approaches [172, 173], but they all have the common strategy of evaluating whether mRNA is a mediator between a SNP and a trait. A variety of approaches are provided elsewhere [162].

6. Gene expression and systems biology-based approaches for the discovery of determinants/signatures of vaccine-induced immunity.

The application of high-dimensional gene expression and/or other omics technologies to reliably identify the determinants/signatures reflecting the development and maintenance of measles vaccine immunity is still in its infancy. Several gene expression studies during the

course of measles infection, or after measles vaccination and/or *in vitro* infection, have provided useful but limited information about the role of specific genes and pathways in the development of measles immunity [62, 174, 175]. Two recent mRNA-Seq studies profiling gene and miRNA expression in the cells of high and low antibody measles vaccine responders have identified essential plasma cell survival and homing factors (e.g., CD93, a key factor for the preservation of plasma cells in the bone marrow and for sustained production of antibodies [176]) and B cell-specific miRNA expression patterns [177] that were associated with neutralizing antibody titer after vaccination.

Systems biology approaches have also yielded important insights into the development of humoral immunity following vaccination. Most systems vaccinology studies focus on the high dimensional analysis of the transcriptome, proteome, metabolome, and/or microbiome. It is equally important to comprehensively evaluate the immune response both in terms of the cell subsets involved and the effector functions produced. This type of approach can be especially useful for pathogens without clearly defined correlates of protection [71], as humoral immunity can be conferred by antigen-specific antibodies with myriad effector functions including: neutralization, complement fixation, opsonization, and enhancement of cellular responses. Each of these effector functions can then be linked to specific gene expression patterns, or "signatures," necessary for their development. Querec et al. were able to identify a gene signature that predicted neutralizing antibody responses to the yellow fever vaccine with 100% accuracy [178]. This signature involved expression of *TNFRSF17*, a gene producing the receptor for the BLyS-BAFF B cell growth factor. A similar study across three influenza seasons found that expression levels of *CaMKIV* were inversely proportional to the titer of hemagglutination inhibiting antibodies [179]. Genomic signatures have also been found to be associated with protection following vaccination with the RTS, S malaria vaccine [180]. Collectively, these and similar studies identify critical pathways necessary for the development of humoral immunity. Further research is needed to identify how these and/or other genes/pathways contribute to measles immunity. The resulting signatures may serve as important predictive biomarkers of immunogenicity or vaccine efficacy.

Novel technologies are allowing researchers to investigate immune responses at an unprecedented level of detail. Mass cytometry (CyTOF®) using heavy-metal conjugated antibodies has expanded the number of parameters one can measure from 12–18 to 40+. This increase in capability enables more comprehensive immune profiling of leukocyte phenotype and higher resolution of functional characteristics (Fig. 2). Similarly, single-cell sequencing (scRNA-Seq) allows us to evaluate individual cellular transcriptomes rather than the average gene expression of all cells in a biological specimen (Fig. 2). One can observe the expression level of transcription factors, cellular receptors, signaling molecules, and other immunologically important genes within relevant cell types [181]. Sequencing of individual T cell and B cell receptors provides information on T/B cell diversity, clonal expansion, and somatic hypermutation [182]. An exciting next step in the field of systems vaccinology will be the combination of multiple single-cell resolution technologies into multi-omics approaches [183]. One example is CITE-Seq (or REAP-Seq), which can be used to simultaneously characterize both surface expression and transcriptome in individual cells, thereby combining the advantages of next-generation sequencing and flow cytometry.

One might use these techniques to assess the individual transcriptomes of tetramer-positive cells in order to gain insights into transcriptional activity in antigen-specific cells [184, 185]. Similarly, scMT-Seq or scTrio-Seq allow for the simultaneous analysis of the genome, transcriptome, and epigenome of individual cells for a comprehensive cell-specific snapshot of genetic landscape and activity [186, 187].

7. Expert commentary.

Given the morbidity and mortality of measles, repeated importations, continuing outbreaks, contraindications to live attenuated measles vaccines for an increasingly immunocompromised population, and unmerited concerns over the safety of the current measles vaccine, it is apparent that new vaccine types are needed.

Unique among vaccine-preventable human pathogens, measles is the most transmissible human disease—requiring at least 90–95% herd immunity for disease control. The current vaccine licensed in the United States has a measurable primary and secondary failure rate that leads to population-level immunity that is often less than that required for herd immunity [17, 49]. This is especially true in regions of the world where seroconversion rates for MMR (and other measles-containing vaccines) are lower than in the United States and Europe.

The ideal measles vaccine, even if parenteral, should induce lifelong immunity after one dose, have little or no contraindications, be manufactured inexpensively, not require a cold chain and be safely stored for long periods of time, and be administered by a variety of health care personnel—particularly in low income countries.

For many of the above reasons, even more appealing would be vaccines that do not require parenteral administration and could be given to infants below the age of 12 months (i.e., no maternal antibody interference), ideally without the need for highly trained health care personnel and suitable for use in low resource settings. In this regard, oral or skin patch vaccines would be ideal candidates if they could be inexpensively made.

To this end, possibilities currently being investigated include protein and peptide-based vaccines using one or more measles viral proteins (H, F, and N proteins and peptides), recombinant protein vaccines, DNA-based vaccine constructs, and virus-vectored vaccines, as well as different delivery systems, such as microneedle skin patch vaccines and aerosol vaccines [107, 117, 188–195]. A unique recently developed administration method is via oral disintegrating films, which have been loaded with measles virus nanoparticles. Early studies in pigs have been promising [196].

8. Five-year view.

Over the next five years, we will continue to see an increasingly sophisticated understanding of measles vaccine-induced humoral immunity. Currently, humoral “measles immunity” is assessed most commonly using either EIA assays or fluorescence-based immunoassays. In research settings, measles neutralizing antibody may also be measured. The former two assays are not direct functional antibody assays and hence can be misleading. Neutralizing

antibody on the other hand, is a direct measure of functional antibody responses, that has been correlated with protection against disease, and therefore, is a better measure of humoral immunity. However, the assay is laborious, expensive, and has lower throughput; therefore, it is not generally used clinically. In addition, our current correlate of immunity/protection is incomplete, as it does not evaluate cellular immune or other parameters that may also be important for durable and/or protective immunity. Systems biology studies are beginning to reveal genetic and molecular "signatures" of protective immune response. In time, it may be possible to narrow such signatures to highly predictive assays of vaccine responsiveness and efficacy/effectiveness, and to identify precise correlates of protection. In addition, protein and antibody array assays may provide a more holistic view of humoral immune response; in other words, they will allow direct measures of antibody response to specific proteins within a pathogen. In the case of measles, for example, we may be able to measure anti-H, anti-F, anti-N, and anti-P antibodies or specific antibody patterns as better correlates of immunity in a high-throughput, low-cost manner. Finally, measures of immune durability are critically needed, and much research is warranted on this topic.

Acknowledgments

Research reported in this publication was supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under award numbers U01AI089859 and R37AI048793. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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9.

Key issues.

- Measles outbreaks continue to occur in high-vaccine coverage and low-measles exposure settings.
- To address the barriers to measles elimination activities and the current knowledge gap, new/additional correlates of protection and new approaches for evaluating and predicting humoral immune response after measles vaccination are needed.
- Genetic determinants of measles vaccine-induced neutralizing antibody response (e.g., *CD46* and *IFI44L* genetic variants, other genetic markers) are under investigation.
- Systems biology and/or other "omics" studies are likely to identify "signatures" of protective and durable immune response after measles vaccination.
- The discovery of predictive "signatures" of measles vaccine immunogenicity, efficacy, and long-term effectiveness will identify individuals in need of additional vaccine doses and/or new improved measles vaccines.

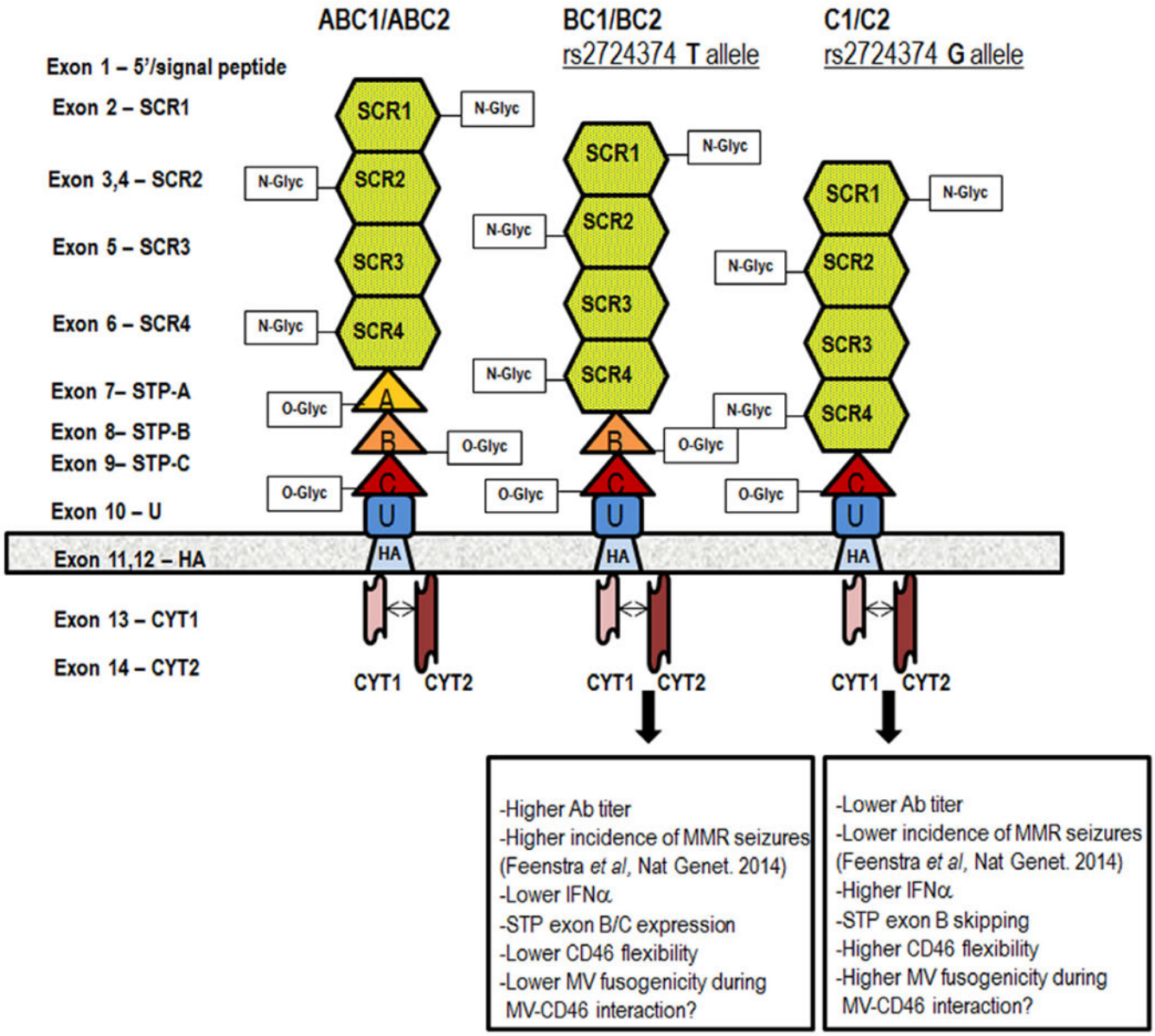

Fig. 1.

Measles virus receptor CD46 and functional effects of *CD46* rs2724374

The figure above is published with permission from Human Genetics. [126, 127] The extracellular portion of CD46 consists of four N-glycosylated conserved short consensus repeats SCR1-4; a STP region that is O-glycosylated (encoded by exons 7/A, 8/B and 9/C); and a region of unknown function (U). The four most common CD46 isoforms are defined based on the present STP exon/exons and the cytoplasmic tail (CYT1 or CYT2): BC1 and BC2 (with B and C exons/domains in the STP and with either CYT1 or CYT2), and C1 and C2 (with C exon/domain in the STP and with either CYT1 or CYT2). The effect of *CD46* rs2724374 on CD46 isoform prevalence (exon B expression or skipping), interaction between CD46 and MV, and immune response following measles vaccination is also summarized for the different genotypes.

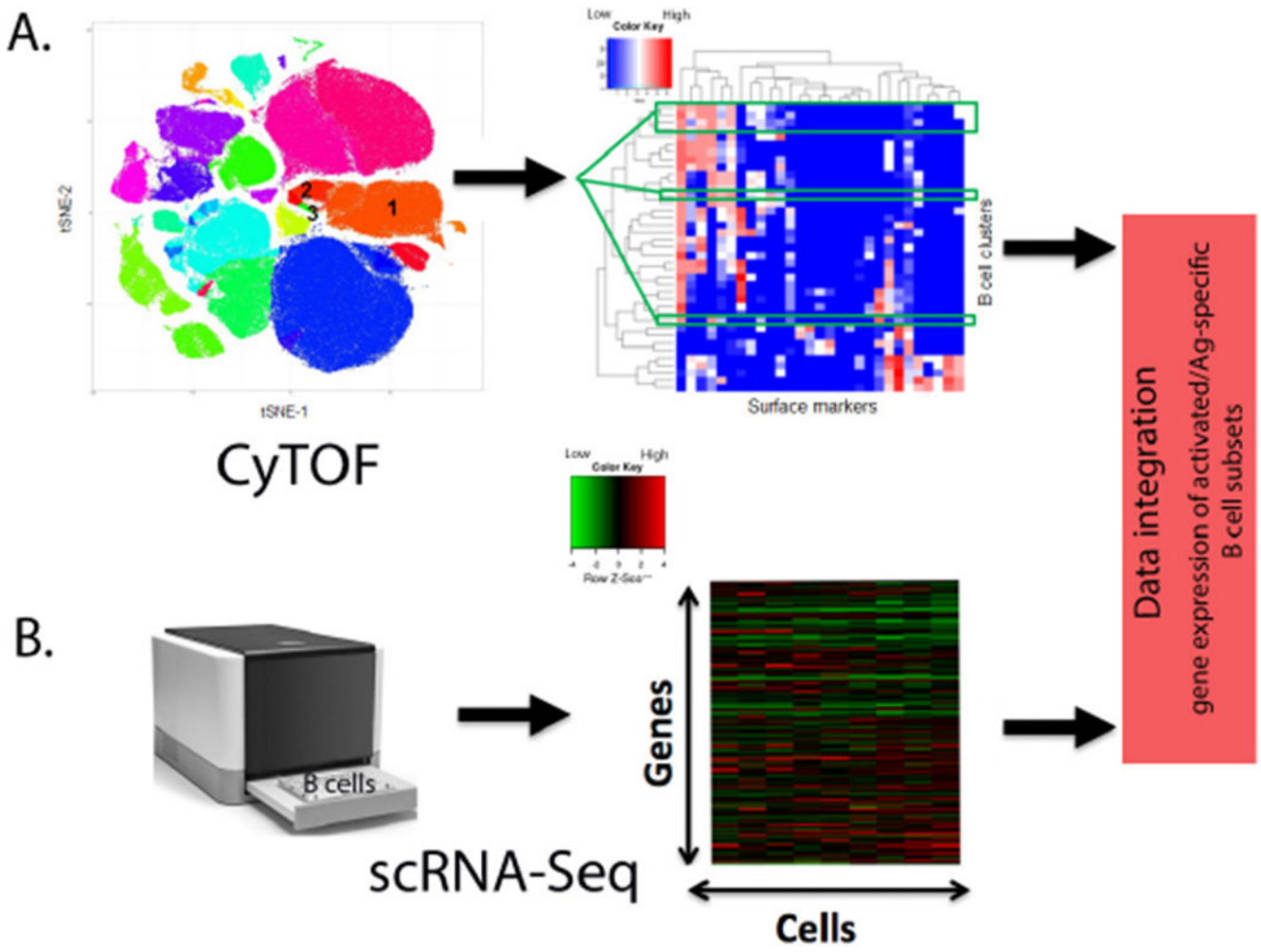

Fig. 2.

CyTOF and scRNA-Seq analysis of B cell subsets after vaccination.

A) Schematic representation of CyTOF. t-SNE plot of cell clusters defined by cellular markers. The annotation of the numbered cell clusters is as follows: 1. naïve B cells; 2. memory B and 3. plasmablasts. For clarity only three of the relevant B cell clusters are shown. Heat map displaying the expression levels (blue=low, red=high) of each cell surface marker in columns and each B cell cluster of interest in rows. B) Schematic representation of scRNA-Seq. Heat map displaying the gene expression levels (green=low, red=high) within single B cells (assay cell input is purified B cells). Data integration allows for the identification of gene expression signatures within activated and/or antigen-specific B cell subsets after vaccination.