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Measles vaccines

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TABLE OF CONTENTS

1. ABSTRACT

Measles is caused by infection with measles virus (MV), a negative strand RNA virus in the Morbillivirus genus of the *Paramyxoviridae* family. Measles is a highly infectious disease of humans spread by the respiratory route and characterized by fever and rash. Important complications include secondary infections associated with MV-induced immune suppression and the neurological disease post-infectious encephalomyelitis. The virus was first isolated in 1954 paving the way for development of the vaccines that have played an essential role in decreasing the worldwide morbidity and mortality due to measles. One of the first vaccines was a formalin-inactivated vaccine that provided only short-lived protection from infection and primed for a more severe disease, atypical measles. This vaccine was withdrawn. The other early vaccine was a live attenuated vaccine (LAV) developed by passage of the original isolate of Edmonston virus through cells in culture, primarily chicken cells. LAV was reactogenic and often given along with immune globulin. Further passage of the Edmonston virus resulted in further attenuation and the well-tolerated vaccines in common use today. LAV is generally given between 9 and 15 months of age. Seroconversion at 9 months is about 85% and at 12 months is about 95%. At younger ages seroconversion is hampered by the presence of maternal antibody and the immaturity of the immune system. The R_0 (numbers of people in a susceptible population that will be infected by one person with the disease) for MV is 15-20 and interruption of endemic transmission of MV in a population requires that >95% of the population is immune. A second dose is necessary to achieve this level and can be given either as a part of a routine immunization program or through periodic mass vaccination campaigns. Research toward improved measles vaccines has focused on development of a vaccine that could be given before 6 months of age, needle-less delivery and heat stability. Several new recombinant vaccines expressing MV proteins have demonstrated induction of protective immunity in macaques and are in various stages of development.

2. INTRODUCTION

Measles is a highly contagious disease of humans characterized by a prodromal illness of fever, coryza, cough, and conjunctivitis followed by the appearance of a generalized maculopapular rash. There is an increased susceptibility to other infectious diseases that is associated with measles virus (MV)-induced immune suppression and responsible for most measles-associated deaths. Despite the availability of a safe and efficacious live attenuated vaccine, measles remains a major cause of morbidity and mortality in children in resource-poor countries and a cause of continuing outbreaks in industrialized nations.

3. MEASLES VIRUS AND ITS REPLICATION

3.1. Virus and viral proteins

MV is an enveloped, nonsegmented, negative-strand RNA virus first isolated in 1954 by Enders and Peebles from the blood of a child with measles (1). MV is a member of the Morbillivirus genus of the *Paramyxoviridae* family that also includes canine distemper and rinderpest viruses, important causes of disease in dogs and cattle. Virions are pleomorphic and range in size from 100-300 nm. The envelope has surface projections composed of the viral hemagglutinin (H) and fusion (F) glycoproteins. The matrix (M) protein lines the interior of the virion envelope. The helical nucleocapsid is formed from the genomic RNA wrapped with the nucleocapsid (N) protein and is packed within the envelope in the form of a symmetrical coil with the phosphoprotein (P) and large polymerase (L) proteins attached.

The N mRNA is the first transcribed from the genome and N is the most abundant of the viral proteins. N binds both to RNA and to P and is required for transcription and replication. The conserved N-terminal portion of the protein is required for self-assembly into nucleocapsids and for RNA binding (2-6). The C-terminal 125 residues are more variable and this domain belongs to a family of proteins with intrinsically disordered regions structurally similar to the acidic activation domains of cellular transcription factors (7-10).

The P protein is a polymerase cofactor activated by phosphorylation that forms trimers and links L to N to form the replicase complex (11). The P gene of MV, like many members of the *Paramyxoviridae* family, encodes nonstructural proteins in addition to P. C is a basic protein translated using an initiator methionine codon in an overlapping reading frame (12). V shares the initiator methionine and the amino terminal 231 amino acids of the P protein, but a non-templated guanosine residue is added through RNA editing that shifts the reading frame to produce a different C-terminus that is cysteine-rich and has zinc-binding properties (13, 14). Neither C nor V is necessary for MV replication (15, 16), but both interact with cellular proteins to regulate the response to infection (17, 18).

H is the receptor-binding protein and an important determinant of cellular tropism. It is a type II transmembrane glycoprotein that resides on the surface of infected cells and of virions as a disulfide-linked homodimer which self-associates to form tetramers. H has a 34 amino acid cytoplasmic tail preceding a single hydrophobic transmembrane region and a large C-terminal ectodomain with a propeller-like structure and 13 strongly conserved cysteines. F is a highly conserved type I transmembrane glycoprotein synthesized as an inactive precursor F_o that is subsequently processed to the active disulfide-linked F_1 and F_2 that cooperate with H for fusion and entry (19).

3.2. Cellular receptors

Two receptors have been identified: membrane cofactor protein (MCP) or CD46 (20, 21) and signaling lymphocyte activation molecule (SLAM) or CD150 (22). CD46 is a widely distributed human complement regulatory protein expressed on all nucleated cells (23, 24). It acts as a cofactor for the proteolytic inactivation of C3b/C4b by factor I (25), but also induces proliferation and differentiation of regulatory T cells (26). SLAM is an important costimulatory molecule expressed on cells of the immune system (27, 28). The cytoplasmic domain has tyrosines and SH-2 domain-binding regions that constitute an immunoreceptor tyrosine-based switch motif (ITSM) that binds small SH-2 domain adaptor proteins important for cell signaling (27-29). Both vaccine and wild type strains of MV can use SLAM as a receptor (28-30). Vaccine strains tend to use CD46 efficiently while wild type strains often do not (28, 30). The receptor binding regions for CD46 and SLAM on H are contiguous or overlapping and most H proteins can bind both receptors, but affinity and efficiency of entry differ (32-36). In general, binding affinity for SLAM is higher than for CD46 (33). Differences in the efficiency of receptor usage may involve interactions with F, in addition to H (37, 38).

MV probably uses at least one additional receptor. The distributions of SLAM and CD46 in tissues do not account for the tropism and sites of MV replication in acute infections where epithelial and endothelial cells, as well as cells of the immune system, are infected (39-42) or in chronic infections where cells of the central nervous system (CNS) are important targets for infection (23, 43). In addition, several *in vitro* studies have shown that infection can occur independent of either CD46 or SLAM (37, 42-44). Receptors used by attenuated vaccine strains adapted to growth in cells from nonsusceptible hosts probably represent an additional category of MV receptors that have not been identified (45).

3.3. Sequence and antigenic variation

Estimates of MV mutation rates range from 10^{-4} to 10^{-3} per nucleotide per year (46). Strains separate into eight different clades (A-H) and at least 23 different genotypes based on the sequence of the variable C-terminal 450 nucleotides of N (47). Identification of genotypes has been useful for analysis of the molecular epidemiology of measles. Several lineages of MV that have characteristic temporal and geographic distributions have been identified (48, 49). Some are localized to specific regions of the world and some are extinct, but most are widely

distributed. Assembly of an increasingly large database of MV genotypes has aided in the identification of global MV transmission pathways and has become increasingly important as control programs are implemented and classification of cases as imported or indigenous is necessary (50).

Although the H gene sequence is variable, particularly in the glycosylation region (51), MV is relatively stable antigenically. Antisera from individuals infected decades ago retain the ability to neutralize current wild type strains of MV and vice versa, although with varying efficiency (52).

4. MEASLES AND ITS COMPLICATIONS

Measles is a human disease that is spread by the respiratory route. There is a latent period of 10-14 days and a 2-3 day prodrome of fever, coryza, cough, and conjunctivitis followed by the appearance of a characteristic maculopapular rash. The onset of the rash coincides with the appearance of the immune response and initiation of virus clearance. Recovery is accompanied by lifelong immunity to reinfection (53) and, in unvaccinated populations measles is typically a disease of childhood. Complications include increased susceptibility to other infections that can cause diarrhea or pneumonia, the autoimmune diseases post-infectious encephalomyelitis and the late persistent CNS infection subacute sclerosing panencephalitis (SSPE). In addition, individuals with deficits in cellular immunity can develop progressive MV-induced giant cell pneumonia or inclusion body encephalitis (54-56).

4.1. Virus replication and spread

MV is spread from infected to uninfected individuals by the respiratory route via aerosol or respiratory droplets. Initial infection is established in the respiratory tract with virus replication in tracheal and bronchial epithelial cells and pulmonary macrophages (57). From the respiratory tract there is extension to local lymphatic tissues, perhaps carried by pulmonary macrophages or dendritic cells (58-60). Amplification of virus in regional lymph nodes results in spread of virus through the blood in monocytes, T cells and B cells to infect a variety of organs (61-63). Lymphocytes and dendritic cells produce little virus unless activated (64, 65).

Primary and secondary lymphoid tissues, including thymus, spleen and appendix, are prominent sites of secondary virus replication (57). MV also spreads to numerous other organs, including the skin, conjunctivae, kidney, lung, gastrointestinal tract, respiratory mucosa, genital mucosa, and liver. In these various sites the virus replicates primarily in endothelial cells, epithelial cells, and monocytes or macrophages (40, 61, 66, 67). Pathologic examination of infected tissues shows multinucleated epithelial giant cells that can also be readily demonstrated in nasal secretions and the conjunctivae during the prodrome and first days of the rash (68, 69). MV-infected epithelial cells are also shed into the urine (68). The initial event in formation of the measles rash is the infection of dermal endothelial cells (70) followed by spread of infection into epidermal keratinocytes (67) and infiltration of mononuclear cells into the area of infection. Epidemiologic data suggest that individuals become infectious for susceptible contacts a few days before the onset of the rash and remain infectious during the rash. During this time virus can be cultured from the nasopharynx, conjunctivae, and mouth (71), suggesting that the respiratory tract is the site of virus release.

5. THE IMMUNE RESPONSE IN RECOVERY AND PROTECTION

The immune responses to MV are important for clearance of virus and recovery from infection, for several of the clinical manifestations of measles and for establishment of long-term protective immunity. The roles of various components of the immune response in recovery from infection have been deduced from the outcome of infection in patients with immune deficiencies and from studies of monkeys (72-75). Although it is difficult to isolate MV after the rash is cleared, MV RNA can be detected for many weeks indicating that complete viral clearance is a prolonged process (73, 76-78). In general, individuals with deficits in antibody production recover, while individuals with deficits in cellular immune responses are prone to slowed clearance and progressive disease.

5.1. Innate responses

MV infection of some types of cells *in vitro* induces production of interferon (IFN)-α and IFN-β, but IFN induction by wild type strains is generally less efficient than by vaccine strains (79). Increased levels of IFN and IFN-induced proteins are detectable in blood after measles immunization (80), but elevated plasma levels of biologically active IFN have not been documented during natural infection (81, 82). MV shuts down IFN production by plasmacytoid dendritic cells, but stimulates IFN production by myeloid dendritic cells *in vitro* (83; 84). Induction of IFN mRNA and protein synthesis may occur at the cell surface through signaling initiated by interaction of the virus with CD46 or toll-like receptor (TLR)-2 or after virus has entered the cell (85-87). MV activates signaling pathways involving the transcription factors NF-κB and IRF-3 (85, 88).

MV replication is sensitive to inhibition by the IFN-inducible protein MxA (89). Although innate responses probably contribute to control of virus replication during the incubation period, the onset of clinically apparent disease coincides with the appearance of MV-specific adaptive humoral and cellular immune responses.

5.2. Antibody responses

Antibodies are first detectable when the rash appears (90-92). The isotype of MV-specific antibody is initially IgM followed by a switch to IgG3 and then, in the memory phase, to IgG1 and IgG4 (90, 93). IgG is initially of low avidity, but avidity increases steadily over several months (94). IgA, IgM, and IgG antibodies to MV are found in secretions and sampling of saliva has provided a noninvasive method for determining immune status (95).

The most abundant and most rapidly produced antibody is to N (92). Because of the abundance of anti-N antibody, absence of this antibody is a reliable indicator of seronegativity. The M protein elicits only small amounts of antibody, except in atypical measles (92, 96). Antibodies to H are the primary antibodies measured by tests based on neutralization of virus infectivity (97, 98). Human convalescent sera show reactivity to linear epitopes, as well as to epitopes dependent on conformation and glycosylation (99-101). Major conformational epitopes have been localized to regions between amino acids 368-396 and in the SLAM-binding region (102, 103). Essentially all of these epitopes are predicted to be a part of exposed surfaces on top of the molecule (102; 104). Antibodies to F contribute to virus neutralization, probably by preventing fusion of the virus membrane with the cell membrane at the time of virus entry (105, 106).

Antibody can protect from MV infection and may contribute to recovery from infection (107, 108). Antibody is sufficient for protection because infants are protected by maternal antibody (108) and passive transfer of immune serum can modify or interfere with measles vaccination and can partially protect children from measles after exposure (109). The best correlate of protection from infection is the level of neutralizing antibody. In infants, the level of maternal antibody correlates with failure of the humoral response to vaccination (108). In outbreaks, antibody levels correlate with protection from disease, with a plaque reduction neutralizing titer (PRNT) of 120 mIU/mL generally considered the level needed (110).

Contributions of antibody to virus clearance are less clear. Failure to mount an adequate antibody response carries a poor prognosis (111) and levels of antibody-dependent cellular cytotoxicity correlate with clearance of the cell-associated viremia (112). Antibody binding to infected cells alters intracellular virus replication and may contribute to control of infection (113-115). However, transient depletion of B cells does not affect virus clearance in infected monkeys (75).

5.3. Cellular responses

The ability to recover from measles was postulated by Burnet to be an indication of the adequacy of T lymphocyte-mediated immune responses (116). There is substantial evidence of a vigorous $CD8^+$ T cell response during infection. MV-specific and proliferating $CD8^+$ T cells with evidence of clonal expansion are detectable in blood at the time of the rash and in bronchoalveolar lavage fluid during pneumonitis (117-122). IFN-γ, soluble CD8 and β2 microglobulin are increased in plasma (121, 123, 124) and $CD8^+$ T cell memory is established by infection (119, 120, 125, 126). Depletion of $CD8^+$ T cells in infected monkeys impairs control of virus replication (74). MV antigens that induce $CD8^+$ T cells include the N, P, H, and F proteins (119, 127, 128). H contains the majority of epitopes recognized by HLA-A2-positive humans (129).

$CD4^+$ T cells are also activated in response to MV infection. $CD4^+$ T cells proliferate during the rash (117) and soluble CD4 is elevated in plasma during acute disease and remains so for several weeks after recovery (130). MV-specific T cell proliferation and production of cytokines, are stimulated during measles (120, 121) and $CD4^+$ T cell memory is established after recovery (128, 131, 132).

MV-specific T cells are responsible for production of a variety of cytokines and soluble factors during disease and recovery. Plasma levels of IFN-γ, neopterin (a product of IFN-γ-activated macrophages) and soluble IL-2 receptor rise during the prodrome, prior to the appearance of the rash (123, 133). This is followed by increases in IL-2 at the time of the rash (121, 124). As the rash fades IL-4, IL-10 and IL-13 increase and elevation of these cytokines persists in some individuals for weeks (121; 124). This pattern of cytokine production suggests early activation of $CD8^+$ (IFN-γ) and type 1 $CD4^+$ (IFN-γ and IL-2) T cells during the rash followed by activation of type 2 $CD4^+$ T cells (IL-4, IL-13) and then regulatory T cells (IL-10) during recovery. IFN-γ may also have an important direct antiviral effect because it can suppress MV replication in epithelial and endothelial cells *in vitro* through induction of indoleamine 2,3 dioxygenase (134).

The cellular immune response is necessary for development of the characteristic measles rash. Biopsies show infiltration of $CD4^+$ and $CD8^+$ T cells and macrophages into areas of virus replication (74). Individuals with deficiencies in cellular immunity may develop measles without a rash (55, 56). MV shedding is prolonged in children with impaired cell-mediated immunity. Giant cells were detected in nasal secretions up to 28 days after the onset of rash in malnourished Kenyan children with severe measles (69) and MV antigen was detected up to 13 days after rash onset in malnourished Nigerian children (135). Prolonged presence of MV RNA has been associated with HIV-1 infection (73) and congenital measles (136).

5.4. Longevity of the immune response

Measles is an acute infection from which there is usually complete recovery and the establishment of life long immunity. Epidemiologic studies of island populations have documented that long term protection from MV re-infection does not require re-exposure to the virus (53). Immunologic memory includes both continued production of antibody (137) and circulation of MV-specific $CD4^+$ and $CD8^+$ T cells (120, 138-140). There is no evidence for persistence of virus, although clearance is slow. Extensive replication of MV in lymphoid tissue may maximize the interaction of viral antigen with antigen-retaining follicular dendritic cells in germinal centers leading to a more robust memory B cell response.

5.5. Immune suppression

Activation of the immune system is coincident with the appearance of immune suppression and both persist for many weeks after apparent recovery. Manifestations of immune suppression include loss of delayed type hypersensitivity responses to recall antigens, such as tuberculin (141, 142), limited *in vitro* lymphocyte proliferation to mitogen stimulation (143) and impaired

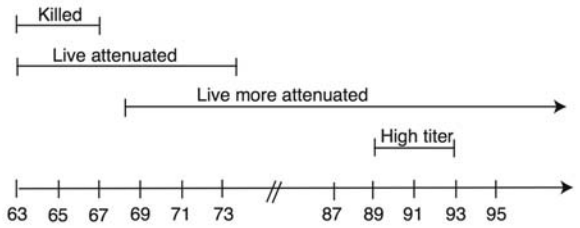

Figure 1. Time line of the development and use of licensed measles virus vaccines.

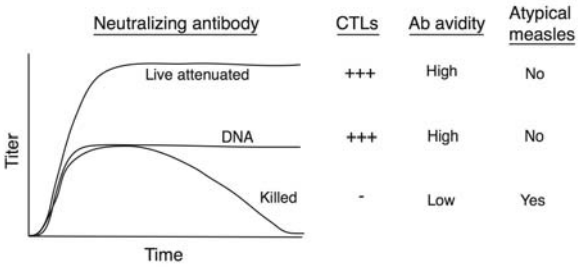

Figure 2. Schematic diagram of the immune responses to different types of measles virus vaccines that are and are not associated with subsequent susceptibility to atypical measles.

cellular and humoral immune responses to new antigens (144). This alteration in immune responses renders individuals more susceptible to the secondary bacterial and viral infections that account for most of the deaths due to measles (145, 146).

Multiple factors probably contribute to immune suppression. Viremia is accompanied by lymphopenia, with a reduction in both $CD4^+$ and $CD8^+$ T cells, that may be due to the death of infected cells or to altered lymphocyte trafficking (147, 148). IFN can suppress T cell proliferation in cultures of MV-infected PBMCs (149). Dendritic cells infected with MV *in vitro* mature poorly, lose the ability to stimulate an allogeneic lymphocyte response and undergo cell death (150). The dominant Th2 response during recovery can inhibit Th1 responses and increase susceptibility to intracellular pathogens (130). The production of IL-12, which is important for the generation of the Th1 response, is decreased *in vitro* following binding of CD46 and is reduced for several weeks in children with measles (151, 152). Conversely, IL-10, which can downregulate Th1 cytokine synthesis and suppress macrophage activation, T cell proliferation and DTH responses, is elevated for several weeks in children with measles (121).

6. VACCINE DEVELOPMENT AND CHARACTERISTICS OF PROTECTION

The isolation of MV in tissue culture by Enders and Peebles opened the way for vaccine development (1). The Edmonston strain of MV was isolated from the blood of a child with measles and successfully propagated in human and monkey cells. Culture of MV led to the simultaneous development of inactivated and live attenuated vaccines (Figure 1).

6.1 Foramalin-inactivated vaccine

Killed MV vaccines were developed using formalin or tween-ether for inactivation of the Edmonson B strain of MV (153). The alum-precipitated formalin-inactivated measles vaccine (FIMV) was given in a 3-dose regimen (153, 154). Recipients of the inactivated vaccine developed moderate levels of neutralizing and hemagglutination inhibiting (HI) antibodies and low levels of complement fixing (CF) antibody (154-156). The vaccine was protective when exposure to measles occurred within several months after immunization (156-158). However, antibody titers declined rapidly, and recipients again became susceptible to measles (157, 159). When infected, these previously FIMV-vaccinated individuals had a tendency to develop a more severe disease, atypical measles (159, 160).

Atypical measles was characterized by a higher and more prolonged fever, unusual skin lesions and severe pneumonitis compared to measles in previously unvaccinated persons (160, 161). The rash was often accompanied by evidence of hemorrhage or vesiculation and began on the extremities rather than the head and trunk. The pneumonitis included distinct nodular parenchymal lesions and hilar adenopathy (162, 163). Abdominal pain, hepatic dysfunction, headache, eosinophilia, pleural effusions and edema were also described. Cases of atypical measles were reported up to16 years after receipt of the inactivated vaccine. Administration of the live virus vaccine after 2 to 3 doses of killed vaccine did not eliminate subsequent susceptibility to atypical measles and was often associated with severe reactions at the site of live virus inoculation (164-166).

Hypotheses about the pathogenesis of atypical measles included an abnormally intense cellular immune response (166), an inability of the inactivated vaccine to induce local respiratory tract immunity (167) and a lack of production of antibody to F which allowed virus to spread from cell to cell despite the development of antibody to H (155, 168). Studies in rhesus macaques have shown that the inactivated vaccine induces a poor cytotoxic T cell response and antibody that does not undergo affinity maturation (169, 170) (Figure 2). Low-avidity antibody can neutralize *in vitro* infection with viruses that use CD46 as a receptor, as routinely measured by PRNT assays in Vero cells, but cannot neutralize infection with wild type viruses that primarily use SLAM (170). This difference in neutralization properties may be due to the higher affinity interaction between MV and SLAM compared to MV and CD46.

Subsequent infection with MV induces an anamnestic antibody response, but the antibody is also of low avidity and cannot neutralize wild type virus. This leads to formation of complexes of non-neutralizing antibody and MV resulting in immune complex deposition, vasculitis and pneumonitis (170, 171). The exact nature of the defect in immune priming exhibited by FIMV has not yet been identified.

6.2. Live attenuated vaccine (LAV)

The process of adaptation of MV grown in primary renal and amnion cells to cells of nonsusceptible hosts, such as the chick embryo, canine and bovine kidney cells, led successfully to the development of LAV strains (172, 176). The first attenuated live measles vaccine was developed by passage of the Edmonston strain of MV in chick embryo fibroblasts to produce the Edmonston B virus (177). Inoculation of this virus into primates produced no clinical symptoms, no detectable viremia and no spread to the respiratory tract (148), but did induce an immune response that protected the monkeys from subsequent challenge with wild type virus (173) (Figure 2).

This vaccine protected children from measles (178) and was licensed in March 1963 (Figure 1). However, Edmonston B LAV induced fever and rash in a large proportion of immunized children (179). Reactions were reduced when immunoglobulin that contained antibodies to MV was given at the same time as the vaccine (109, 180, 182). More extensive passage of the Edmonston B virus in chick embryo fibroblasts produced the more attenuated Schwarz vaccine (182) that currently serves as the standard measles vaccine in much of the world. The Moraten strain used in the United States is closely related to the Schwarz strain (183). Other Edmonston-derived vaccine strains (e.g. Zagreb, AIK-C) and attenuated strains developed independently (*e.g.* CAM, Leningard-16, Shanghai-191) are also successful vaccines (184-187). Few differences have been described among MV vaccine strains (all genotype A) regardless of the geographic origin of the parent virus (183). However, there may be some biologic differences. Edmonston-Zagreb is produced in human diploid cells, rather than chick embryo fibroblasts, and may be more immunogenic in young infants and when delivered by the aerosol route (188).

The lyophilized vaccine is relatively stable, but the reconstituted vaccine rapidly loses infectivity. LAV is inactivated by light and heat, and after reconstitution loses about half of its potency at 20^{o}C and almost all potency at 37^{o}C within an hour (189). Therefore, a cold chain must be maintained for the vaccine prior to and after reconstitution. LAVs replicate less efficiently than wild type MV (148, 190), but induce both neutralizing antibody and cellular immune responses qualitatively similar to that induced by natural disease, although antibody titers are lower (178, 191). Antibodies first appear 12-15 days after vaccination and peak at 1-3 months. In many countries, LAV is combined with other live attenuated virus vaccines such as those for mumps, rubella (MMR) and varicella (MMRV). These measles-containing vaccines have proven safe and effective and have saved the lives of many millions of children (192, 193).

The recommended age of vaccination varies from 6 to 15 months. The probability of seroconversion and the amounts of antibody induced are determined by the levels of persisting MV-specific maternal antibody and the age of the infant at the time of vaccination (109, 194-197). Levels of passively acquired antibody are dependent on the mother's level of antibody, on the transfer of antibody across the placenta and on the rate of antibody decay in the infant (198). The cellular immune response is induced while the antibody response is impaired in young infants with maternal antibody (195). As measles is controlled in a region, an increasing proportion of mothers will have measles immunity induced by vaccination rather than natural infection. This will result in lower levels of passively acquired antibody in infants and the possibility of lowering the age of vaccination (199-202). Currently, the proportions of children that develop protective levels of antibody are approximately 85% at 9 months of age and 95% at 12 months of age (196). The recommended age of vaccination varies regionally and is a balance between the optimum age for seroconversion and the probability of acquiring measles before that age (196). In areas where measles remains prevalent, measles vaccination is routinely performed at 9 months, whereas in areas with little measles, vaccination is often at 12 to 15 months. During epidemics and in human immunodeficiency virus (HIV) type 1-infected infants in developing countries, vaccination at 6 months is recommended with a second dose at 9 months (203).

LAV is administered subcutaneously or intramuscularly. However, there is substantial interest in alternate routes of delivery that would not require needles and syringes. Neither oral nor intranasal administration is effective (204; 205), but respiratory delivery may be more promising. There are several ongoing efforts to develop and evaluate aerosol delivery of aqueous and dry powder forms of LAV (188, 206, 207). Aerosol administration was advocated by Albert Sabin in the early 1980s, is highly effective in boosting pre-existing antibody titers and may hold promise for use in older children (188, 208, 209). Respiratory routes of vaccination have also been advocated as a means to lower the age of immunization (208, 210). However, the primary immune response to aerosolized measles vaccine is lower than it is to subcutaneous administration of the same vaccine (211, 212). The reasons for this are not known, but may be related to dose or efficiency of delivery and infection.

Genetic background affects the likelihood of seroconversion and antibody titers (213-215). Common childhood illnesses at the time of vaccination may also have an effect (216). Any potential decrease in seroconversion must be balanced against the loss of the opportunity for vaccination and the consequent risk of the child acquiring measles. Similar compromises must be considered with respect to immunizing individuals infected with HIV-1 (217). Overall, measles vaccine has been well tolerated in HIV-infected children and adults, although the antibody response is lower and progressive fatal infection has occurred occasionally (218-222). Because of the potential severity of wild type MV infection in HIV-infected individuals (223, 54), LAV is recommended for routine administration to infants without respect to HIV-1 infection status in most countries, but, in the US is not recommended for those with known low $CD4^{+}$ T cell counts (224). LAV is also contraindicated in individuals with severe deficiencies of cellular immunity because of the possibility of disease due to progressive pulmonary or CNS infection (225-227).

The dose of MV routinely used for immunization is between 10^3 and 10^4 plaque-forming units. Overall, the efficacy of a single dose of measles vaccine in infancy is estimated at 80-95% (195). When ten- to 100-fold higher doses were used, seroconversion in younger infants improved and in 1990 the WHO recommended use of the high-titer Edmonston-Zagreb (EZ) vaccine at 6 months of age in countries in which measles before the age of 9 months was a significant cause of death. However, subsequent follow-up of children receiving high-titer vaccines in countries with high childhood mortality showed an increased mortality in girls over the subsequent 2 to 3 years and this recommendation was withdrawn (228-230). Mortality was not due to measles, but rather to a relative increase in the deaths due to other infections (231). The pathogenesis of delayed increased mortality after the high titer vaccine is not understood but occurred primarily in those who developed a rash after vaccination and may be related to long-term suppression of immune responses similar to that induced by measles (232) or alteration of immune responses associated with a change in the sequence of delivery of vaccines (233-235).

The duration of vaccine-induced immunity is variable. In general, levels of antibody are lower after vaccination than after recovery from natural disease and MV-specific antibody and $CD4^+$ T cells decay with time (178, 236-238). Secondary vaccine failure rates have been estimated to be approximately 5% at 10 to 15 years after immunization, but are probably lower when vaccination is given after 12 months of age (239-241). However, decreasing antibody titers do not necessarily imply a complete loss of protective immunity, as a secondary immune response usually develops after re-exposure to MV, with a rapid rise in antibody titers without overt clinical disease (239). These secondarily infected individuals may constitute an epidemiologically protected, but infectious, population of individuals (242).

7. CONTROL OF MEASLES WITH THE CURRENT VACCINE

7.1. Measles epidemiology in the absence of vaccination

Measles is one of the most infectious of communicable diseases. It is estimated that 76% of household exposures of susceptible persons lead to measles (243) and that the basic reproductive number (R_o) or average number of secondary cases produced by an infectious individual in a totally susceptible population, is 15-20 (244). Transmission is most efficient through direct exposure to an infected individual, but MV can survive for hours in respiratory droplets, and direct contact is not required. Individuals are most infectious from 4-5 days before through 4 days after the appearance of the rash (245).

There is no animal reservoir and no evidence of latent or epidemiologically significant persistent infection in humans (246). Therefore, maintenance of MV in a population requires a continuous supply of susceptible individuals. Because older members of a community are immune through previous exposure to the virus, endemic measles is primarily a disease of childhood. If the population is too small to establish endemic transmission, the virus cannot be maintained (247). Mathematical calculations and studies of islands and cities with populations of different sizes have shown a requirement for a population of 250,000-500,000 to establish measles as an endemic disease (248, 249).

In large population centers, measles is endemic with occasional epidemics as the numbers of susceptible individuals increase. These epidemics spread in waves from large cities to smaller cities and then to rural areas over time (250). In temperate climates measles is more frequent in the winter and early spring. Epidemic frequency is determined by the number of susceptible individuals, the duration of infectiousness and patterns of population mixing (249). The size of the population is also a primary determinant of the age of seroconversion. The average age of infection is earlier in urban than in rural areas in both developed and developing countries (228). In developing countries with large populations, high birth rates lead to infection at an early age. Very young infants are protected from measles (and from response to vaccine) by maternal antibodies. The duration of protective antibody in the infant is dependent on the level of maternal antibody, a primary determinant of the level of antibody in the infant at birth. The source of maternal immunity (vaccine vs. natural measles), gestational age, and presence of maternal infections such as HIV and malaria, are determinants of the amount of antibody passively transferred and, therefore, the length of time required for initial levels of antibody to decay to the point that an infant will become susceptible to measles (198).

7.2. Routine vaccination with a single dose

Prior to the widespread use of measles vaccine, measles was estimated to result in 5-8 million deaths each year. The decline in mortality from measles in developed countries can be attributed to improved nutrition and medical care, but mostly to effective delivery of LAV. In developing countries, routine delivery of vitamin A has also contributed to decreased case fatality ratios for measles (251, 252).

Routine infant immunization with LAV alters the epidemiology of measles by reducing the numbers of susceptible individuals in the population. In countries with high rates of vaccination the average age for measles is increased because herd immunity reduces transmission and indirectly protects young children from infection. Vaccination also lengthens the time between epidemics (228). When outbreaks occur in areas of sustained high vaccine coverage an increasingly large proportion of the cases will be in older individuals who are susceptible due to primary or secondary vaccine failure (253). Outbreaks become increasingly likely to be local and dependent on social networks (254).

7.3. Development of a two-dose vaccination strategy

Because of the high infectivity of MV and the fact that not all individuals develop protective immunity following vaccination, a single dose of measles vaccine

does not achieve a sufficient level of population immunity to eliminate endemic MV transmission. More than 95% of the population needs to be immune to interrupt endemic transmission. Ninety-five percent coverage with a 95% response rate will only achieve a level of population immunity of 90%. Therefore, to achieve 95% immunity, a second dose of vaccine is necessary to immunize persons who missed or did not respond to the first dose (217, 255-257). The 2-dose strategy has been credited with elimination of indigenous measles in many countries in which it has been employed (217).

Two broad strategies to administer the second dose have been used. In countries with sufficient infrastructure, the second dose can be delivered as a part of routine vaccination, typically prior to the start of school with school entry requirements enforcing the policy (258). A second approach, first developed by the Pan American Health Organization (PAHO), involves mass supplementary immunization campaigns to deliver the second dose of vaccine in a wide geographic area (259). The PAHO strategy consists of four subprograms: Catch-up, Keep-up, Follow-up and Mop-up. The Catch-up phase is a one-time, mass-immunization campaign that targets all children in a broad age group (typically 1-14 years) regardless of measles disease or vaccine history. The goal is to rapidly achieve a high level of population immunity and interrupt MV transmission. If successful, these activities are cost effective and can result in dramatic declines in incidence and mortality (192). Keep-up refers to maintenance of routine infant measles vaccination. Follow-up involves periodic mass vaccination of 1-4 year-olds to prevent the accumulation of susceptible children and Mop-up campaigns target children that are difficult to reach.

However, even highly immunized populations in countries that have eliminated endemic transmission are vulnerable to localized outbreaks associated with importation from areas where measles remains endemic (50).

8. DEVELOPMENT OF NEW VACCINES

A new vaccine would be advantageous if it would allow vaccination of infants before 6 months of age. This would both close the "window of susceptibility" between decay of maternal antibody and vaccination and facilitate delivery by allowing measles vaccine to be given at the same time as other WHO Expanded Program for Immunization (EPI) vaccines. Additional motivations for development of a new vaccine would be to increase thermostability, to avoid the use of needles and syringes for delivery and to provide a vaccine that would be safe for immunocompromised individuals (260).

However, development of new vaccines has been hampered by an incomplete understanding of protective immunity and of the priming for enhanced disease by the inactivated vaccine. In addition, the lack of a good small animal model has impeded study of protective immunity and efficient testing of novel vaccine approaches. Nevertheless, a number of experimental vaccines have been developed and vaccination with individual MV proteins expressed in plants, viral or bacterial vectors, or as DNA, peptides or proteins have been explored in animal models such as mice and cotton rats (261, 262, 263). However, macaques are the most relevant model system because they allow assessment of immunization in the face of maternal antibody, of vaccine-induced protection from challenge, and of the potential for a vaccine to prime for enhanced disease (106, 169, 265-268).

8.1. DNA

Delivery of viral genes into host cells for processing and antigen presentation without the need for virus infection, along with thermostability, inexpensive manufacture and the potential for mucosal administration, make DNA vaccines an attractive possibility for development. In mice, naked DNA expressing H or F delivered by gene gun or intramuscularly induced humoral and cellular responses (269, 270). Immunization with DNA expressing N did not protect against intracerebral challenge with rodent-adapted MV (271). Delivery of naked DNA by various mucosal routes induced a cytotoxic T cell response that was potentiated by co-administration of cholera toxin or cationic lipids as an adjuvant (272). DNA-prime, oral protein-boost strategies have also shown some promise in mice (263). DNA expressing H has also been mucosally delivered to cotton rats using vaccine strains of *Salmonella* or *Shigella* and induced neutralizing antibody and T cell responses (273). Challenge after 3 doses showed reduced lung titers in the immunized animals.

Several DNA vaccines have been tested in juvenile cynomolgus and rhesus macaques. Transdermal delivery of 2 doses of plasmids encoding MV proteins elicited low serum antibody responses. On challenge 1 year later, there was evidence of immune priming with more rapid antibody and cellular immune responses and a tendency for lower viremia in immunized, compared to naïve, animals (274). Intradermal (500 μg) or gene gun (8 μg on gold beads) delivery of two doses of DNA encoding the H protein, F protein or both elicited cytotoxic T cell responses and sustained, but low titer, antibody responses in rhesus macaques (106). Protection from challenge 2 years after the initial immunization correlated with the levels of neutralizing antibody at the time of challenge. All monkeys having antibody levels of <120 mIU/mL (one immunized with F, one with H and one with H + F) developed a rash and viremia. However, the rashes were mild and there was no suggestion of atypical measles. Monkeys with intermediate levels of antibody developed viremia without a rash and monkeys with high levels of antibody did not develop a viremia. These studies indicated that DNA vaccines could protect from measles and did not predispose to atypical measles.

Studies of the same or similar vaccines in infant macaques have shown induction of lower levels of antibody, particularly in the face of maternal antibody, and limited protection from challenge (265). Therefore, DNA vaccines will need to be improved if further development is contemplated. Subsequent studies have focused on using

adjuvants to enhance the immunogenicity of DNA vaccines and more reliably exceed the threshold of antibody needed for complete protection. These adjuvants have included cytokines such as IL-2 (275) and formulation with complex carbohydrates or lipids designed to improve immune responses by increasing DNA entry into cells or by providing a depot for prolonged release of DNA (276-280).

8.2. Subunit proteins

Recombinant proteins expressed in insect, plant or mammalian cells and proteins purified from MV have been used for vaccine development. Early studies showed that immune-stimulating complexes (iscoms) that incorporated the F and H proteins into a matrix with quilaja saponins, phospholipids and cholesterol stimulated HI and hemolysis-inhibiting antibodies in mice (281). Immunized mice were protected from intracerebral challenge with a hamster neurotropic strain of MV (282, 283). In cynomolgus macaques, these iscoms induced durable MV-specific antibody in the presence and absence of passively transferred antibody and provided partial protection from challenge (284, 264).

8.3. Vectored by other viruses or bacteria

Several viruses have been used to express MV proteins and tested as experimental vaccines. The first studies were done with vaccinia virus expressing H and F. This vaccine was not able to stimulate an antibody response in the presence of passively acquired antibody, but did provide partial protection presumably mediated by the observed MV-specific T cell responses (264, 285). Subsequently, studies of the replication defective modified vaccinia virus Ankara (MVA) expressing H and F showed that 2 doses of 10^8 pfu delivered intramuscularly and intranasally 1-2 months apart elicited neutralizing antibody and T-cell responses in juvenile cynomolgus, but not infant rhesus, macaques in the presence and absence of passively transferred antibody (267, 285). These monkeys were at least partially protected from challenge 3-12 months after vaccination. MVA-based vaccines have been shown to be safe in immunosuppressed macaques (286).

Sindbis virus-based alphavirus replicon particle vaccines expressing MV H induced high-titered, dose-dependent, MV neutralizing antibody after a single vaccination in mice. Vaccination of juvenile rhesus macaques with a single dose, and infant macaques with two doses, of 10^8 particles induced sustained levels of high-titered MV-neutralizing antibody and IFN-γ-producing memory T cells. Most monkeys were protected from disease, but not from viremia when challenged 18 months later (76). However, newer versions of this vaccine using chimeras of Sindbis and Venezuelan equine encephalitis replicons expressing H and F were fully protective (Pan *et al*, unpublished data).

Recombinant Bacille-Calmette-Guerin, the mycobacteria used for neonatal immunization against tuberculosis, has been engineered to express the MV N protein and used to immunize infant rhesus macaques (287). Cellular immune responses were elicited, but provided only partial protection from MV challenge. Monkeys developed systemic infection, but lung inflammation was reduced.

9. POTENTIAL FOR MEASLES ERADICATION

The global elimination of measles has been debated since the 1960s when measles vaccines were first licensed (288). The 1997 Dahlem Conference on Disease Eradication defined eradication as the permanent reduction to zero of the global incidence of infection with the consequence that interventions would no longer be necessary. Criteria deemed necessary for a disease to be eradicable were: (1) humans must be crucial for transmission, (2) sensitive and specific diagnostic tools must exist, and (3) an effective intervention must be available. Interruption of transmission in a large geographic area for a prolonged period supports the feasibility of eradication. Measles is thought by many to meet these criteria (259, 289).

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