Measles Incidence and Eradication

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Measles is an RNA virus infectious disease mainly seen in children. Despite the availability of an effective vaccine against measles, it remains a health issue in children. Although it is a self-limiting disease, it becomes severe in undernourished and immune-compromised individuals. Measles infection is associated with secondary infections by opportunistic bacteria due to the immunosuppressive effects of the measles virus.

measles immunity vaccine

1. Measles Virus

Respiratory droplets and small aerosol particles transmit the measles virus. The virus has a high affinity for lymphocytes, and it was shown in transgenic mouse models that the virus infects the alveolar macrophages and dendritic cells of the lungs in just 2 days [1][2]. The infection starts in the lower respiratory tract before it progresses towards the upper respiratory tract. The virus also spreads to the skin, conjunctiva, and other organs. These particles remain suspended for 2 h [3]. The measles virus has an incubation period of 10 to 14 days. Infected patients exhibit coryza, cough, and conjunctivitis at the end of the prodromal phase. Koplik spots in the cheeks follow this, and a rash spreads from the face to the toes [2]. The onset of fever occurs around 10 days after infection and usually lasts for 7 days [2].

Endemic measles virus transmission shows a specific seasonal pattern [1]. Measles outbreaks happen mostly during late winter and early spring. The seasonal outbreak is supported by social contact patterns, such as increased individual contact between school children and the typical environmental factors favouring viral transmission in temperate climates [4]. Measles outbreaks are more variable in tropical regions [5]. During the initial months after birth, infants are protected from measles infection by the maternal anti-measles virus IgG antibodies that are received passively from the mother [3]. The infants born to women with naturally acquired immunity against wild-type measles virus infection are less susceptible to measles infection than infants born to women with vaccine-induced immunity due to higher titres of anti-measles IgG in women infected with the wild-type measles virus [6][7].

The average age of measles infection depends on factors such as the decline in maternal immunity, contact patterns, and age of acquired immunity against measles infection. With an increase in the vaccine coverage and

prevention of contact between infected persons and the healthy population, the age of measles infection has shifted from infancy to adolescence and adulthood [8].

The measles virus belongs to the genus Morbillivirus. It is a member of the Paramyxovirinae subfamily and the family Paramyxoviridae. It is an enveloped, single-strand, non-segmented, negative-sense RNA virus. The virus manufactures pleiomorphic viral particles ranging from 150 nm to 900 nm [9]. Like other viruses belonging to the morbilliviruses, the measles virus is highly contagious and is spread via the respiratory route [10].

The viral RNA genome is 15,894 nucleotides long and encodes for six structural proteins and two non-structural proteins. The structural proteins are the nucleocapsid protein (N), the matrix protein (M), the phosphoprotein (P), the haemagglutinin protein (H), the fusion protein (F), and the polymerase protein (L). The two non-structural proteins are V and C, encoded by the P gene, which is instrumental in modulating the cellular response to infection [11][12]. While the virus exits the host cell, the virus takes up the cell membrane of the host cell, forming the virus's envelope. This envelope acquired from the host cell helps the virus evade the host cell's immunity. Interior to the envelope is the matrix made up of a protein called M. The genomic RNA is surrounded by a helical nucleocapsid protein (N). Special proteins L and the phosphoprotein P help in the replication of the viral genome and making copies of the virus. The haemagglutinin (H) and fusion (F) glycoproteins form the surface projections on the envelope. These two glycoproteins interact with or without additional cellular proteins (receptors) that help the virus bind and enter into immunological cells, such as lymphocytes, monocytes, macrophages, dendritic cells, and the epithelial cell adherens junctions [11]. These proteins determine the viral specificity for different cell types and tissues. Infection with measles imparts life-long immunity against the virus due to the production of IgG antibodies and memory cells against the haemagglutinin protein that blocks the binding of the virus to the host cell receptors [13].

On the other hand, the fusion protein helps the virus enter the host cell by enabling the fusion of the viral envelope to the host cell membrane [14]. Based on the sequence of the variable region of the nucleoprotein, 24 different strains of the measles virus have been identified by the WHO [15]. Many of these measles virus genotypes are no longer detected in the infected population [16][17]. Despite the genetic diversity, the measles virus is antigenically monotypic. An attenuated measles vaccine derived from the Schwarz and Moraten measles vaccine strains that belong to a single genotype is still protective against measles [2]. The measles virus is an RNA virus with a high mutation rate, giving rise to evolving viral strains. Since the vaccines for the measles virus are directed against the highly conserved epitopes of the haemagglutinin protein, there is no need to develop vaccines against the new evolving strains of the measles virus [18].

2. Immunological Aspects of Measles Infection and Host Immunity

2.1. Innate Immunity Response to Measles Infection

The measles virus spreads through its mobility, starting from the site of infection to the respiratory tract, lymphoid organs, and then back to the respiratory tract. It first infects CD150-expressing cells, namely, the dendritic cells (D.C.s) and macrophages (M.P) (Lemon et al., 2011). D.C.s play a central role in developing an immunological response to pathogens by presenting antigens on major histocompatibility complex molecules (MHC), T-cell activation due to costimulation of CD80, and CD86, which ultimately leads to the release of proinflammatory cytokines IL-12 and IL-18. The production of IL-12 by D.C.s is important for the optimal activation of CD4+ and CD8+ T cells. The activation of the CD4+ and CD8+ cells is initiated by interferon-gamma (IFNγ). This is crucial as it activates the innate immune response to infection and reactivates during the pathogen reencounter [19].

2.2. Overwhelming of Innate Immune Response by Measles

The measles virus can block the production of IL-12 by using the Fc-gamma receptor pathway [20]. The Fc-gamma receptor (FcγR) belongs to the Fc portion of IgG, and it is heavily involved in modulating immune responses [21]. This mechanism is thought to be involved with the interaction of the viral N protein with the FcγR molecules on the surface of D.C.s, ultimately leading to lower production of IL-12 [20]. The exact mechanism of how it happens is not yet that clear. Alternatively, the complement regulator protein CD46, in conjunction with the H glycoprotein of the virus, is known to downregulate the IL-12 secretion further [20][22].

Reducing IL-12 levels after any active measles infection prevents T cell activation and differentiation, which lowers immunity. The H protein, especially in wild strains, can also trigger the activation of Toll-like receptors (TLR1, TLR2, and TLR6) and myeloid differentiation protein 88 (MyD88) on the D.C.s and MP [23]. This might lead to the activation of nuclear-factor-activated protein (NF-kB), which can regulate the expression of CD150, along with other cell surface receptors. CD150 upregulation might increase infection in cells exposed to the measles virus [24]. This can also contribute to the development of MeV infection. NF-kB is also involved in the expression of inflammatory cytokines (IL-12, IL-6, IL-18, IL-1β), chemokines (C-X-C motif chemokine ligand 8 or CXCL-8), and tumour necrosis factor alpha (TNFα) [25]. These interplay mechanisms highlight the role of D.C.s in the measles-induced immunosuppression early on in the infection stages. A lack of optimal T cell activation can generate suboptimal T cells that are instrumental in the upregulation of CD150, allowing for measles virus entry, migration to the lungs, and propagation in the host cells [26]. Neutrophils and granulocytes, among other cells, respond to the viral infection by producing IL-12 and will skew the T cell responses [27]. This could also cause a reduction in the interactions with the major histocompatibility complex molecules (MHC) and the stimulation of T cells.

The early stages of infection with wild-type measles virus are highlighted by secretions of TNF and IFNγ [28]. Elevated levels of IL-4 and IL-10 cytokines are seen in the later stages of infection [29][30], and they could lead to immunosuppression [31]. The measles virus causes a loss of memory B and naïve cells and delays reconstitution of these B cells, leading to immune amnesia [32]. Although the loss of B cells and the infection contribute significantly to immune amnesia, the interactions between the measles virus and D.C.s also contribute to lower immunity. D.C.s' role in B cell education is a well-known fact [33]. They are involved in activating the CD4+ T cells and then guide them through their differentiation into T follicular regulatory (Tfr) or T follicular helper (Tfh) cells. The Tfh cells, in conjunction with follicular D.C.s (FDCs), contribute towards B cell selection in the germinal centres of lymph

nodes, leading to the formation of long-lived plasma cells (LLPC), which are crucial in the production of antibodies. Although the host immunity is initially severely affected by the measles virus, the infection surely produces anti-measles immune responses quickly [10][34]. The lymphopenia produced by the measles virus is short-lived and quickly replaced by lymphocytes specific to the measles virus. This clearly shows that the D.C. functions are momentarily blocked.

2.3. Innate Immunity Responses at the Cellular Level to the Measles Virus

The type-I IFN system is a cell-intrinsic immune response that consists of multiple pathways that lead to upregulation of the IFN proteins (IFNα or IFNβ) and subsequent activation of the Janus kinases, signal transducer, and activator of transcription proteins (JAK-STAT) pathway [35]. IFNγ1, -2, and -3, which constitutes the type-III IFN system, also detect the measles virus [36]. Even though their signals are sent through a different receptor, the downstream signalling pathway is identical to that of the type-I IFN system [37]. Thus, both type-I and type-III systems work in conjunction to activate the innate immune responses in the mucosal tissues. The measles virus, which is a double-stranded RNA (dsRNA), is detected through various cytoplasmic RLRs (retinoic-acid-inducible gene-1-like receptors) that include RIG-I, laboratory of genetics and physiology (LGP2), and melanoma differentiation gene-5 (MDA-5) [38][39]. Activating the MDA5/RIG-I receptors leads to the binding to mitochondrial anti-viral signalling adapter (MAVS). This binding leads to an activation cascade involving TANK-binding kinase 1 (TBK1), interferon regulatory factor 3 (IRF3), and NF-kB [37]. Transcription factors of NF-kB and IRF3 play an essential role in the expression of IFNβ. TLR3 and TLR7 play an important role in producing type-1 IFN as soon as they detect the dsRNA or ssRNA in the endosomes [40]. IFNα is expressed via the activation of the IRF7 via the TLR7 signalling pathway, which depends on the MyD88/IKKα [40]. IFNα and IFNβ attachment to the type-1 IFN receptor (IFNAR) results in an IFN signalling cascade. The signalling cascade further activates the Janus kinases (JAK1, tyrosine protein kinase (TYK2)) and phosphorylation of STAT1 and STAT2 proteins. Janus kinases and STAT proteins then combine with interferon regulatory factor 9 (IRF9) to form an interferon-stimulated growth factor 3 (ISGF3), which then helps in the expression of interferon-stimulated genes (ISGs) [41].

2.4. Measles Virus Evading the Host's Immunity Mechanisms

The measles virus has evolved an extensive immune evasion mechanism. It interferes with IFN responses, making the IFN system the most important innate and adaptive immunity [42]. The measles virus belongs to the genus *Morbillivirus* of the *Paramyxoviridae* family [43]. The genome of the measles virus encodes for eight viral proteins N-P/V/C-M-F-H-L [44]. The measles virus genes attack all the parts of the IFN system right from their induction to their signalling cascade. The P/V/C gene in the measles virus expresses proteins P, V, and C, which form the main antagonists to the IFN system. The V protein mainly targets cellular proteins [31]. The V protein is characterised by the amino n terminal and carboxy-terminal domains [42][45] The carboxy-terminal of the V protein binds tightly to the STAT2 protein, thereby inhibiting the IFN signalling pathway [35][46][47].

On the other hand, the amino-terminal domain of the V and P proteins binds with STAT1 [48][49]. However, the binding needs the presence of STAT2 to make it efficient [47]. The phosphorylation of STATs is also blocked by the

V protein [50]. In short, the measles V protein blocks the STAT activation. The V protein also targets MDA-5 through the charged residues on the carboxy-terminal of the V protein [51]. V protein also targets RIG-I and LGP2 receptors, effectively blocking any chances of RLR activation [52].

2.5. Infection and Host Immunity

Host immune response is responsible for the neutralisation of the virus and the establishment of immunity for further infections [48]. The viral proteins V and C inhibit the expression of interferons in the host cells facilitating the replication and spread of the measles virus [53]. It is followed by the action of cellular and humoral immunity.

Adaptive immunity is responsible for the recovery and establishment of long-term protection against measles virus infection. The first antibodies formed against the measles virus are the IgMs formed at the time of rash. IgMs stay in the bloodstream for 6–8 weeks. Detection of IgM in the bloodstream by enzyme-linked immunosorbent assays (ELISA) is used to confirm measles virus infection [54]. Subsequently, IgG antibodies against the measles virus are formed. Among the IgGs formed, the most abundant IgGs are formed against the viral nucleoprotein [55]. Cellular immunity is essential for viral clearance and recovery.

Weak or deficient innate and adaptive immune responses can result in severe measles infections and sequelae of events leading to secondary infections. Measles infection is the first immunosuppressive viral infection described [34]. Transient lymphopenia occurs during measles infection due to the migration of the lymphocytes from the bloodstream to the lymphatic tissues, the primary sites of measles virus proliferation [10][56][57]. Studies showed abnormal cellular immunity during measles infection, such as a declined lymphocyte proliferation and an inhibited function of dendritic cells [58]. These studies were conducted in ex vivo conditions. Therefore, it is not clear whether these immunosuppressive activities of the measles virus infection also apply in the in vivo conditions [59].

3. Diagnosis

While diagnosing a suspected measles patient, clinicians should consider the typical clinical features of measles infection and look for the secondary problems due to measles infection, such as pneumonia, conjunctivitis, otitis media, and diarrhea. Since malnutrition, especially vitamin A deficiency, immune deficiency (HIV infection), and immunosuppression (individuals undergoing organ transplantation), are major contributors to measles-associated mortality, a thorough clinical examination and a detailed history of patients should be taken. Patients with these risk factors are at a higher risk of mortality. Prompt action by clinicians is warranted in patients with vitamin deficiency, which involves administering vitamin A supplements to these patients. The hospital administration should take appropriate action to isolate the measles-infected cases to prevent the transmission of the measles virus to healthy individuals [60]. It is challenging to clinically diagnose measles infection before the appearance of the rash and in immunocompromised children who might not have the rash. Furthermore, it is challenging to diagnose measles infection in individuals who had acquired antibodies against measles from the maternal immune system or through previous vaccination, in cases of mild illness, and in cases with less evidence of a rash [39].

The most widely employed laboratory test detects IgM specific for measles virus antigens by ELISA. The levels of measles-virus-specific IgM are very low or undetectable till 4 days after a rash appears. Therefore, tests within 4 days of rash development give false-negative results [61]. Almost all the measles-infected individuals show detectable levels of measles virus-specific IgM after 4 days of rash appearance, and 75% of measles-virus-infected individuals show detectable levels of measles-virus-specific IgM within the first 3 days of rash appearance. IgM levels specific to the measles virus are highest during 1–3 weeks post rash onset and decline to undetectable levels within 4–8 weeks post rash onset [62].

4. Clinical Presentation

Measles is a self-limiting acute contagious viral infection. It is characterised by a typical rash, high fever (up to 104 °F), cough, coryza, and conjunctivitis. Characteristic white lesions called Koplik's spots form in the buccal mucosa even 1–2 days before the appearance of the rash; therefore, Koplik's spots can indicate measles infection, even before the appearance of the rash. A flat red rash appears first on the face and the neck and subsequently advances to the trunk and the extremities in solid and discrete spots within 3–4 days after the onset of fever. Children with previous immunisation history present minimal rash and sometimes do not show the typical characteristics of measles infection, i.e., cough, coryza, and conjunctivitis [63]. Malnourished children present with a prominent, deeply pigmented rash [10]. As a rash is a result of innate/cell-mediated immunity, in conditions of compromised cellular immunity, e.g., HIV, a measles infection may not develop a rash, or the appearance of the rash may be delayed. Generally, in uncomplicated cases of measles infection, the recovery takes place within 1 week of rash appearance [64]. Several factors complicate measles infection, affecting most organs. The factors contributing to the complication of measles are young age (infants), age older than 20 years, pregnancy, malnourishment, vitamin A deficiency, and immunocompromised conditions [65].

Owing to its immunosuppressive effects, measles infection results in several secondary infections by opportunistic bacteria and viruses. The respiratory tract is the primary system affected by secondary infections following a bout of measles infection per se. Measles infection per se can cause Hecht's giant cell pneumonia [52]. Pneumonia can also result from secondary bacterial and virus infections, accounting for a significant proportion of measles-associated mortality. The other most frequent respiratory complications associated with measles infection are laryngotracheobronchitis (croup) and otitis media. Bacterial and protozoan infections secondary to measles infection also led to diarrhoea, which is a major contributor to the morbidity and mortality associated with measles infection [50].

Kerato conjunctivitis was a leading cause of blindness due to measles infection. The measles vaccine and vitamin A supplementation have decreased the incidence of blindness caused due to kerato conjunctivitis from measles infection. Measles during pregnancy may result in low birth weight, spontaneous pregnancy loss, and maternal and prenatal mortality [66].

The measles virus also infects the central nervous system (CNS). It results in three rare conditions in the CNS, viz., acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE), and subacute

sclerosing panencephalitis (SSPE). The major clinical presentations of ADEM are fever and seizures. It is a demyelinating autoimmune disease [9]. The incidence of ADEM is 1 in 1000 individuals infected with measles and can develop within days to weeks of infection. MIBE is an active brain infection resulting in neurodegeneration and mortality in individuals with compromised cellular immunity, such as children who received organ transplants and HIV-infected patients [67].

5. Management

Measles is a self-limiting viral infection. The management regime involves therapies to control/manage the associated risk factors and complications, such as dehydration, malnutrition, or nutritional deficiencies. The management of measles depends on prompt diagnosis, treatment of bacterial and viral infections secondary to measles infection, and vitamin A supplementation [68].

Vitamin A supplementation can be given to measles patients in order to reduce the measles-associated complications and mortality rates [69]. Vitamin A deficiency impacts the severity of measles since it slows recovery; it may cause measles-related problems, such as blindness; and may be linked to a higher death rate [70]. The American Academy of Pediatrics (AAP) and the WHO advocated for vitamin A treatment for hospitalised children with measles [69]. Compared with a single dose, two doses of vitamin A supplements have been shown to reduce the risk of measles-associated mortality in children younger than 2 years [15]. Vitamin A supplements should be given in two doses every 24 h to all children diagnosed with measles. This medication may help to avoid eye damage and blindness by restoring low vitamin A levels during measles infection, which can occur even in well-nourished children. Supplementing with vitamin A was also demonstrated to minimise measles fatalities [69]. However, recent studies suggested that vitamin A was not utilised correctly to treat US children with measles, either because it was not administered at all or because it was taken at too low levels [69][71].

Because measles has a long incubation period before viremia appears, there is a large window for antiviral therapy. Rapid antiviral therapy, in particular, might completely prevent infection onset in naive patients. However, since a clinical condition follows the peak of viral multiplication, protracted incubation periods may limit therapeutic potential. Although there is no effective and specific anti-viral therapy for the measles virus, some studies have shown promising results with anti-viral agents, such as ribavirin and interferon alfa in severe measles cases [36][72].

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