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Review Article

Understanding the Measles Virus at 70 Years: From Cellular Mechanisms to Immunisation, 1954-2024

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Measles virus (*Morbillivirus* abbreviated as MV, but more recently MeV) is the causal agent of Measles disease, thought to have existed at least 4000 years ago, affecting predominantly infants, but also immunocompromised individuals and others remaining a public health issue today globally. In this review, we are discussing the historical background about MeV infection to modern–day research, then delving into Measles disease and discussing what is known about immunisation against the disease. We elucidate what is known about the viral structure and the function of the viral proteins. The genomic stability of the MeV particle is suggestive that the third pathogen with the potential to be eradicated (after the Variola and Rinderpest viruses) requires further biological and immunological clarification. Here therefore covers a bow from structure and mechanism to clinical aspects of MeV infection touching topics like cellular receptor–associated factors to the immunology of MeV infection. We highlight the actual knowledge about innate immune response during MeV infection, including chemokine and cytokine expression finalised by the current understanding of adaptive immune responses to MeV.

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Introduction

Comparatively less is known of the underlying cellular immunological mechanisms of natural Measles virus (MeV) infection's innate and adaptive immune responses in humans; initially because the original wild-type (wt) MeV isolation occurred in 1954 alongside concurrent use in immunisation, which continued thereafter. This first isolation was known as the "Edmonston strain" derived from

David Edmonston, a student at Fay School, which led to the first Measles vaccine developed shortly after. Other relevant biological discoveries occurred prior and simultaneously As early as 1869, Friedrich Miescher documented DNA isolates, then named "nuclein". Synthesis of nuclein by white blood cells (WBCs), known as leukocytes, was noted to contain the elements carbon, nitrogen, and hydrogen with phosphorous in abundance, but not sulphur ^[1]. Miescher later contracted tuberculosis, but laid the foundations for future research.

Measles disease is defined as caused by the species *Measles Morbillivirus* infecting only humans. The causal virion is defined biologically within the taxonomical system by order *Mononegavirales*, family *Paramyxoviridae*, genus *Morbillivirus* and species *Measles Morbillivirus*; but another *Morbillivirus*, the Rinderpest virus (RPV), was the second virus reported to be eradicated globally prior to 2011, known as a cattle plague ^[2]. This was preceded by Variola virus (VARV) eradication, the causal agent of Smallpox disease in humans confirmed during 1980 ^{[3][4]}. Immunisation utilising MeV was tested in 1948 with the licensing of two vaccines in 1963 which were composed of a live attenuated virus (LAV), derived from MeV, superseding in this instance simultaneous development of a withdrawn formalin–inactivated MeV vaccine strain ^{[5][6][7]}. Both were aimed at evoking a host immunogenic long–term response against the first *Morbillivirus* known to cause human disease ^{[5][6][7]}.

In 1948, a pioneer Mark Adams ^[8] examined how seven bacteria and/or viruses could be inactivated through gas/liquid exchange through bubbling nitrogen over *Escherichia coli*. It was then observed that a preventative chemical could restrict cellular replication, causal of pathological conditions ^[8]. Other pioneers such as Crick and Watson further clarified the nuclear structure of DNA in 1953; while various groups grappled and advanced this through experimental investigation. Debates occurred with arguably the key theoretical framework, in 1961, outlined by Jacob and Monod ^[Q] of the role of messenger molecules, now known as mRNA, in gene regulation and protein production ^[10]. Therefore, during this period it could be seen that primary chemical structures influence leukocytes traversing restrictive cellular barrier layers known as the glycocalyx and the endothelial surface layer (GC–ESL). Secondly, viral antigens can be restricted during replication within the respiratory tract, vascular (endothelial) and epithelial cellular layers ^[11]. Thirdly, WBCs (also called immune cells) develop and evoke specific phenotypes permeating throughout the vascular system. This occurs through inhibitory and stimulatory proteins, as well as autocrine and paracrine hormonal cellular messengers ^[12].

and cells. Most can be analysed through genetic and tissue expression effecting the host immune response which can predispose a person to different infections or cancer.

Measles disease was considered to be causal of more than 2 million deaths each year in 1980 (see Supplementary materials). Around 1981, as research evolved, Bellini et al. ^[13] published the first article discussing how this occurred through the host immune reactivity with the purified MeV haemagglutinin (H) protein stimulating immune cells to recognise a protein expressed by the MeV virion. Throughout the 20th century, guidelines were produced by the World Health

Organisation (WHO), and many countries now utilise a routinely scheduled Measles containing vaccine (MCV), also known to counter Mumps virus (MuV) as well as the Rubella virus (RuV), known as the trivalent MMR in routine immunisation programmes to reduce the prospective rate of incidence and severity of MeV–evoked disease (see Supplementary materials) ^[12]. Host cell presentation of peptides called antigens through immunisation could thus stimulate the rate of immune system recognition to facilitate the rate of immune response to prevent multiple diseases.

Thirty-seven years later (2017), MeV disease mortality estimates remained around 140,000 individuals per year with variable infection/mortality rates globally, and in resource-limited countries. It is considered that environmental factors contributed to the decrease in the severity of MeV infection besides immunisation ^[14,]. The rate of severe Measles disease is affected by a myriad of factors. The same family of *Paramyxoviridae* also encompass the Nipah virus (NiV), which, similarly to MeV, can cause severe neurological disease, as well as blindness, brain damage and encephalitis in a minority of infections ^{[5][15][16][17][18]}. Potential explanations to elucidate this further during past, present, and future research are discussed.

The lack of antigenic variation of MeV is suggestive that eradication potential is possible. The significance of this review is that it provides key insights into MeV infection in both natural infection as well as studies of immunised individuals since MeV isolation. Furthermore, the effects of MeV proteins within cellular transduction are examined here based on many years of research. Therefore, the wider public health community will be able to explain further the importance of immunisation in prophylaxis against Measles disease.

Background to modern-day measles research

History of Measles disease

There is no description of Measles disease in the works of Hippocrates and Galen, although the disease may have been reported in Indian texts several centuries before. Most likely Measles disease was misdiagnosed with other exanthematic diseases ^[19]. The first detailed description distinguishing Smallpox disease from Measles disease was by Rhazes (865-925 AD), a chief physician at a hospital in Baghdad ^[4,]. Measles disease was considered to be widespread in Europe, Asia, India, and China in the Middle Ages. With the discovery of America and European colonial expansion from the 17th century onwards, Measles spread from the Renaissance period to the 20th century becoming a global public health issue ^{[4,][19]}.

Monovalent measles immunisation began in 1963, and was shown as prophylactic, with indications MeV immunisation could reduce infection and disease severity ^[20]. A team at Boston Children's Hospital comprised of John Franklin Enders, together with Dr. Thomas C Peebles, isolated MeV. The individual infected patient blood serum sample was obtained from an 11–year–old boy during an outbreak in Boston, Massachusetts. Alongside Samuel Katz, and notably a pioneer Maurice Hilleman, who worked at Merck and Co., this led to the development of the first LAV ^[15]. A further MCV was developed in 1968, with the combined MMR vaccine following in 1971 which is utilised to counter antigens expressed by MeV, MuV and RuV ^[15].

In 1974, the WHO introduced MCV into its expanded program of immunisation (see Supplementary materials) ^[5]. Even though Measles is one of the most contagious infectious diseases ever (Ro range 12–16), population immunisation coverage of 95% is considered to be prophylactic through reducing viral infection transmission rate triggering epidemics ^[5]. The first vaccine developed by Enders' team was derived from the MeV Edmonston–B strain, with this LAV having high antigenic stability, explaining remarkable efficacy, regardless of the MeV genotype ^[21]. A large decrease in disease incidence was observed since, and during cell culture, less virulence was observed. Retention of the ability of immunisation to induce a strong immune response with neutralising antibodies (nAbs) against MeV was also observed ^[21].

Subsequently, serial MeV passage in chick embryo fibroblasts (CEFs) yielded other attenuated vaccine strains denoted as "Moraten and Schwarz" inducing fever and rash in 10% of those immunised ^[22].

Comparison of protein sequences of the H protein, together with fusion (F) and nucleocapsid (N) coding genes of MeV vaccine strains occurred thereafter through the Edmonston–Zagreb (EZ) strains of slightly different lineages. Human **fibroblasts derived from lung tissue** diploid cell lines, (WI–38), were also used for cell passage, which is the vaccine strain most widely used in resource–limited countries ^[5]. Vaccine strains used were also derived from the chorioallantonic membrane–70 cell line (CAM–70), whilst others were named after the place of research including Leningrad–16, Shanghai–191 as well as AIK–C, each of which are closely related to MeV genotype A viruses with few sequence differences ^{[5][23]}. Below is shown the chronology since initial MeV isolation (see Figure 1)



Figure 1. Evolution of 19th and 20th century MeV vaccine utilised strains. Virus schematic was adapted from ViralZone, SIB Swiss Institute of Bioinformatics (<u>https://viralzone.expasy.org/86</u>), licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.

The first MCV dose is administered as a single dose at 9–12 months of age followed by a second in routine schedules varying globally, but immunisation with two dose regimens is usual ^[5]. The trivalent MMR vaccine is licensed for use in the United States of America (USA) and many other countries in the 21st century ^[15]. Universal immunisation, in the case of MeV, led to an overall decline in global incidence quantified as a 66% reduction (145 to 49 cases per million population between 2000 to 2018), concurrently accompanied by reduced Measles disease mortality reduction of 73%

(535,600 to 142,300 individuals) ^[24]. These figures are notable. Currently, immunisation against MeV can be administered as MCV, MMR, or a recent formulation including a chickenpox component (known as MMRV, with V abbreviating the Varicella Zoster virus, VZV) ^[25]. The COVID–19 pandemic led to setbacks in surveillance and immunisation efforts. The interruption/disruption of routine immunisation services has left millions of children vulnerable to preventable diseases like Measles. Around 22 million infants globally missed at least one dose of a MCV throughout routine immunisation schedules in 2022 whilst other outbreaks around the globe did occur ^{[4][16][26][27][28]}.

Measles disease and immunisation

Immunisation against MeV is considered to induce long-term cellular immunity; however, less is explained about the underlying biological mechanisms of how this occurs [5][29]. Since isolation, the attenuated MeV through cell-expressed antigens is utilised as an LAV through its ability to infect cells and evoke the required cellular immunogenic response without Measles disease manifestation ^[5]. Attenuated MeV is being evaluated to target other viral antigens expressed by Human Immunodeficiency virus (HIV), Dengue Fever virus (DENV), and Chikungunya virus (CHIKV), discussed elsewhere ^{[30][31]}. Furthermore, potential applications could probably include MeV as an oncolytic viral (OV) vector therapeutic (around 2022), with evaluation occurring for future potential treatment for cancers like glioblastomas [32][33][34][35]. The original LAV strain of MeV infects host cells using receptors. Characterised are at least three receptors which MeV employs. These are the cluster of differentiation (CD) molecule CD46, as well as CD150, but also nectin -4 ^[36]. The latter is a member of the immunoglobulin (Ig) superfamily and is known as a type I membrane adhesion molecule, recently becoming recognised. This could be a cellular checkpoint that can shed its extracellular domain promoting angiogenesis by regulating the C-X-C chemokine receptor 4 (CXCR4) and C-X-C motif chemokine ligand 12 (CXCL12) axis [37][38][39]. The attenuated MeV strain could also have similarities to both Vaccina virus (VACV) and modified vector versions utilised to counter VARV leading to Smallpox disease eradication prior [4].

Measles disease affliction generally can affect different ages, but particularly vulnerable infant populations and immunocompromised individuals [40]. Throughout 21st century vaccine development, efficacy was indicated in 2002 of more than 95.4% studied in individuals (n = 471) seroconverting and producing nAbs against MeV [41]. The efficacy and safety of MMR immunisation

were the subject of debate in the 21st century [42]; however, 2021 reports summarising population real–world data suggest efficacy of more than 90% to either the trivalent (MMR) or quadrivalent (MMRV) immunisation options [5][43]. More recently, it has been indicated that MeV immunisation achieves nearly 98% seroconversion, generating antibodies predominantly neutralising the conserved H protein of the attenuated MeV vaccine strain [44][45][46][47][48][49].

The terms vaccination and immunisation are derived from VARV research together with the VACV ^[4]. Research now only occurs with the latter evoking active prophylactic immunological responses in a host animal or human ^[4]. Active immunity is commonly used to describe the process of exposing a host to an antigen and can be natural or acquired; similarly, passive immunity can be either natural or acquired. The two terms are historically used to differentiate between types of host immune responses with the first utilised that may be long–lasting following infection or immunisation ^[50]. The second passive type of immunity refers to the transfer of antibody types in hosts, for example, IgG, or similar other licensed preparations like Rabies Ig (RIG), as well as monoclonal antibody (mAb) preparations ^[51]. Different proteins utilised in research and viral vector vaccine development can be a beneficial factor in priming the innate and adaptive immune system cells to effect an immunogenic response reducing the severity of pathogenic infection ^[35]. This occurs through many immune cell phenotypes now known ^[28]. Longevity and kinetics of antibody production by B cells are factors, alongside T cells adequately stimulating a recall memory immune response to MeV infection throughout illnesss.

Structure and mechanisms of MeV

The MeV virion particle size is 15,894 kilobases (kb) from the 3' end of the negative (-ve) sense single-stranded RNA genome ^{[44,][52]}. This encodes the nucleoprotein (N), followed by a conserved tetrameric H protein, fusion (F) protein, matrix (M) protein followed by a trimer of **phosphoproteins (P) combined with two non-structural proteins (**C/V) with a larger polymerase (L) enzyme towards the 5' end of the RNA genome ^[44,]. The L protein polymerase sequentially transcribes through binding to MeV RNA at the 3' leader sequence with polyadenylation occurring during synthesis with V protein produced through RNA editing and a P protein synthesised from the C protein. This process utilises host intracellular machinery for the RNA-dependent RNA polymerase (RdRp) to transcribe and produce proteins to produce the infectious virion. Viral attachment of the virion occurs through the

MeV H protein attaching to cell receptors, with the F protein facilitating entry via the cellular phospholipid–rich plasma membrane (PM) where viral mRNA is capped and polyadenylated within cellular cytoplasm ^[53]. Therefore H protein nAbs evoked by attenuated MeV is the first key mechanism of restricting viral entry. MeV virions traverse cell membranes and replicate intracellularly within cell cytoplasm, followed by cell egression ^[54]. Below is depicted the timeline history of the discovery of selected *Paramyxoviridae* (see Figure 2).



Figure 2. Structure of MeV and historical *Paramyxoviridae* isolation.; HPIV; human parainfluenza virus; hMPV: human metapneumovirus; OH: hydroxyl group Viral schematic was taken from <u>https://viralzone.expasy.org/86;</u> SIB Swiss Institute of Bioinformatics, licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.

In 2019, it was indicated that the MeV virion forms inclusion bodies (IBs), without a membrane, with three MeV abundant N, P, and L proteins ^[55]. The MeV P was demonstrated to act as a chaperon and cofactor for the L protein, with a third multimerisation domain (MD) affecting gene expression of MeV ^[4,7]; whilst the M protein of *Paramyxoviridae* is known to direct virion assembly interacting with cell membrane phospholipids like phosphatidylserine (PS) and phosphatidylinositol 4,5– bisphosphate (PI(4,5) P₂) that could be potential therapeutic inhibition targets, facilitating the spherical or filamentous protrusions formed during viral egress ^[45]. However, in 2020 fluorescence studies highlighted the N and C–terminal P domains through liquid–liquid phase separation (LLPS)

structures without a membrane before fusion, forming nucleocapsid–like particles that RNA molecules can localise with regards to MeV ^[56].

Historical aspects of MeV characterisation

Genetic characterisation of the MeV virion indicates ancestry before 1915, with the H protein conserved, explaining why current diagnostics and therapeutics remain relevant for MeV infection prophylaxis and reducing potential pathophysiology ^[57]. Mutation rates of MeV were estimated in 1999 at 9 x 10^{-5} per base/replication with a genomic mutation rate of 1.43 per replication cycle indicating point mutations comparable between other -ssRNA viruses, including Poliovirus as well as Vesicular Stomatitis virus ^[58]. Genomic sequencing classifies viruses based on nucleotides. To this effect, MeV clades were originally classified before 2011 designated by letter (e.g., A to H), known as clades, with 24 genotype sequences designated by a number (e.g. B3, H8) ^[59]. It was recommended by the WHO that 450 nucleotides encoding the carboxyl (-COOH) amino-acids (aa) of the nucleocapsid (N) protein would be used to assign the genotype ^[60].

Between 2007 and 2015, protein epitope prediction and molecular mapping have remained in ongoing development for the immune system to be trained as more responsive [61][62][63]. During a host immune response, fragments (epitope peptides) are presented and processed through two classes of major histocompatibility complex (MHC type I/II), encoded by the human leukocyte antigen (HLA) utilised by antigen–presenting cells (APCs). The APCs include dendritic cells (DCs), monocytes and macrophages (M ϕ) amongst a network of other characterised immune system cells [16][28][64].

A summary of genomic sequencing reports spanning 2005 to 2014 denotes that the predominant detected MeV strains in surveillance were B3, D8, and D4, with predominantly H1 whilst two others were monitored (G3/ D9) (see Supplementary materials). Subsequently, in 2015, MeV antigenic stability was further attributed to inflexible F and H proteins indicating that MeV generates a host polyclonal antibody response against both F and H proteins [46]. At the same time in 2015, sporadic outbreaks in Canada occurred of MeV H1 and D8 genotypes [65]. Shortly thereafter in 2018, circulation of predominant MeV genotypes were confirmed as decreasing to four [66]. These were denoted as B3/D8, together with two others (D4/H1) during 2020 [66]. Out of these, two (B3/D8) are known to be endemic across six of the WHO regions. To this effect, continuing surveillance in Italy between 2015 to 2019 documented MeV genotypes (n = 1273) submitted to the Genbank database [67][68]. These reports

utilise H as the genotype to identify MeV in line with WHO guidelines $\frac{[67]}{1}$. Comparisons with prior MeV genotypes during this MeV sporadic outbreak found unique details of one MeV genotype, B3, where alanine was substituted by valine (denoted as B3 A400V) $\frac{[67]}{1}$. It was crucially uniquely indicated that within this MeV B3 clade, 62% of individuals affected by MeV had been immunised prior $\frac{[67]}{1}$. The significance remains unknown at the date of writing. Furthermore, the other MeV D3 clade had an amino acid (aa) substitution to threonine, seemingly within the MeV H noose epitope (HNE) $\frac{[61][67]}{1}$. The authors describe epitopes in common that are targeted by the immune system including a receptor–binding epitope (RBE), a sugar–shield epitope (SSE), a loop epitope (LE), as well as a neutralising epitope (NE) $\frac{[61][67]}{1}$. The HNE conformation (379–400 aa) within MeV forms an epitope region characterised by three cysteine residues with a surface–exposed loop where the epitope can be recognised by antibodies produced by B cells $\frac{[61][67]}{1}$. In 2023, further genotyping indicated that D8 was the prevalent MeV strain in circulation in a small sample $\frac{[69]}{1}$. Many protein mutations can affect immunologically programmed responses to pathogens discussed below.

Clinical aspects of MeV infection

Measles disease is now rarer than in the 20th century, with immunisation programmes implemented in many countries together with ongoing genotype surveillance (see Supplementary materials). It remains a preventable contagious infection, with one vaccine dose usually given at around 12 months of age, followed by a second between 18 months to around 4 years of age (see Supplementary materials) ^[70]. The prodromal stage can be flu–like, accompanied by rising fever, coryza, cough, conjunctivitis and fatigue ^[70]. Often there is a visible epithelial cell rash, although occasionally not, however examination of the buccal mucosa can show white "Koplick" spots. The classic blotchy, slightly raised red rash (non-itchy) can appear (day 3 to day 7) with symptoms lasting for a further 7 days by becoming flat with drier skin accompanied by skin colour change as the rash sheds [70]. Management is mostly symptomatic, with fever and fluid management as the main targets, plus rest and avoidance of strong light. This reduces the risks of complications occurring like pneumonia, acute encephalitis and the devastating longer-term outcome of sclerosing panencephalitis, and is almost fatal [48]. Confirmation of diagnosis is usually clinical, alongside testing sera for IgM or IgG, with the former appearing first, whilst the latter levels rise after symptom onset. Measles disease during pregnancy can increase the risk of miscarriage or preterm labour, largely due to the high fevers seen with this infection and the LAV is also not given during pregnancy ^[70]. Complications of MeV infection may be pronounced in immunocompromised and poorly nourished individuals. Such complications include otitis media (ear infection), pneumonia (lung infection), encephalitis (inflammation of the brain), as well as meningitis (inflammation of the lining of the brain) [48]. Cells that are infected by MeV include endothelial cells (ECs), neurons and astrocytes, which causes delayed persistent inflammation through MeV infection instigating central nervous system (CNS) symptoms [48]. Such complications in 2015 were considered defined by four categories; namely MeV encephalitis, acute post–MeV encephalitis, MeV IB encephalitis, and subacute sclerosing panencephalitis [48]. The latter is a lesser observed phenomenon, but each is a serious and potentially fatal clinical phenomenon and is specified by incidence within the range of 6.5 to 11 individual cases per 100,000 MeV cases following most commonly infant MeV infection [48].

Immunology of MeV infection

MeV cellular-receptor associated factors

Measles cellular infection was investigated after immunisation with the attenuated MeV to occur through CD46, known as a membrane cofactor protein (MCP) discovered in 1986 ^[20]. Canadian and French research in 1993 by groups led by Dörig ^[71] and Naniche ^[72] showed MeV required CD46 for binding, fusion and replication, but could be inhibited by two types of antibodies ^[73]. The two types of antibodies are mAbs as well as polyclonal antibodies defined by protein specificity. Therefore, CD46 is considered the initial adhesive entry receptor MeV employs as a ligand for cellular entry across the PM with MeV H and F proteins required for syncytia formation ^{[72][73]}. It is considered that CD46 is expressed by many nucleated cells ^[73]. During 2010, clarification of CD46 extracellular structure domains elucidated interaction with complement proteins as depicted below, through the crystal structure complexed with human adenovirus type 11^[74]. This is depicted below (see Figure 3).



Figure 3. A depiction of CD46 structure and role during MeV infection. C3b: complement factor 3b; IL–10: interleukin 10; CD25: cluster of differentiation 25; T_{REG}: regulatory T cell. Viral schematic was taken from <u>https://viralzone.expasy.org/86</u>, adapted from ViralZone, SIB Swiss Institute of Bioinformatics. The Figure was partly created with Servier Medical Art (<u>https://smart.servier.com/</u>), licensed under a Creative Commons Attribution 4.0 Unported license.

CD46 can be activated and is expressed within the myeloid cellular lineages binding to complement proteins (C3b/C4b), a crucial part of coagulation system pathways. Antibodies synthesised by B cells in response possess more than two domains with an antigen binding receptor (Fab) domain recognising pathogenic epitopes, together with a crystallizable fragment (Fc) protein domain structure. The latter effector Fc receptors [Fc₇RI (CD64), Fc₇RII (CD32) and Fc₇RIII (CD16)] are crucial in effector cell function ^[75]. These affect antibody opsonization (binding) through cellular membrane receptors effecting an immune response through signalling, and homeostatic complement regulation synthesizing fibroblast growth factors (FGF), as well as angiogenic factors regulating vascular growth. Knowledge of this was less well known then, however, the CD46 receptor usage is demonstrated to be preferentially expressed during oncogenic disorders and is described as a "pathogen magnet" in various infections ^{[73][76]}. Therefore, CD46 is localised with many proteins that enhance FGF necessary for angiogenesis during common skin and systemic viral infections affecting the vasculature through different organ systems ^[77]. During 2002 other research *in vitro* did indicate that the MeV H protein uses other receptors to determine cell specificity ^[77].

Many MeV sporadic outbreaks have occurred since isolation. It is now known that MeV infects WBCs called lymphocytes, expressing the second receptor known as signalling **lymphocytic activation molecule 1** (SLAMF1, CD150) ^[78]. The SLAMF1 receptor is expressed by activated B cells, T cells, DCs and monocytes (see Supplementary materials). This second receptor, SLAMF1, is considered to be expressed throughout the primary immune system organs (bone marrow/thymus), secondary (spleen, tonsils, lymph nodes), as well as tertiary lymph systems (e.g., bronchus–associated lymphoid tissue, BALT), but also by platelets and haematopoietic stem cells (HPSC) ^[78].

Nectin-4 (poliovirus-receptor-like 4, PVRL4) is a third receptor of relevance during MeV infection, overexpressed in specific tumour carcinomas (breast, lung, colorectal, pancreatic, ovarian cancer), and is usually expressed at lower levels during infancy when MeV infection frequently occurs ^[79]. Nectin -4 clarification came as recently as 2012, similar to poliovirus receptors (PVR) like CD155 [80] [81][82]. The others are individually considered as nectin-1 (CD111), an entry factor receptor for Herpes Simplex virus (HSV-1/HSV-2), with nectin-2 (CD112) an entry factor of Human Herpes viruses (HHV), whilst nectin -3 (CD113) was also characterised $\frac{[83]}{2}$. Nectins are classified as an Ig superfamily glycoprotein similar to antibodies mediating cell-cell adhesion. As recently as 2014, Mateo et al. [38] did indicate that specific loops of nectin-4 govern MeV H protein attachment. Crucially nectin-1 was then implicated to form a part of this adhesive mechanism, but also forming a heterodimer with nectin-4 with the MeV H protein competing at this interface $\frac{[38]}{2}$. However, MeV also infects airway epithelial cells lacking SLAMF1 ^[84]. Nectin–4 regulation could be controlled during the cell cycle usually expressed at low cell membrane levels but could be inhibited. Furthermore, DC-SIGN can cross-link with host antibodies at the cell plasma membrane surface $\frac{[84]}{2}$. Nectin-4 protein is also used as a counterpart specifically expressed on certain subtypes of cells including DCs [79][80][85]. Each of these was characterised using X-ray diffraction between 2007 to 2013 with 25 known structures relevant to understanding MeV pathogenesis (see Supplementary materials). In 2022, an initial report yet to be peer-reviewed potentially clarifies that immune cells are affected directly through draining lymph nodes (dLNs) within the tonsils $\frac{[86]}{100}$. Nectin-4 is concurrently considered a ligand for the inhibitory lymphocyte receptor (T cell immunoreceptor with Ig and immunoreceptor tyrosine–based inhibitory motif domains, TIGIT) expressed by both T cells and NK cells [87][88].

In 2011, the first report appeared describing a fourth receptor of relevance in the context of other nonpathogenic or pathogenic Phleboviridae (Uukenimei virus / Rift Valley fever virus). This is known as the DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN, CD209). Recent data indicates this receptor RNA is predominantly located within specifically two types of APC, namely classical and intermediate monocytes (see Supplementary materials). Its corresponding ligand (CD209L) is indicated to have comparatively high RNA expression within fibroblasts and ECs according to data on protein atlas (see Supplementary materials). Just prior in 2007, DC-SIGN was shown as a relevant trigger on DCs that could be induced involving Toll-like receptors (TLRs) via acetylation of the nuclear transcription factor p65 leading to activation of the nuclear factor kappa**light-chain-enhancer of activated B cells** (NF- κ B) ^[89]. Reports show that this serves as an adhesive receptor facilitating virion internalisation, as well as uptake via endocytic pathways for MeV entry [84]. It was shown in the years following 2016 that mAbs inhibit MeV cellular entry and resulting disease, through binding to CD46, SLAMF1 and nectin $-4 \frac{[61]}{1}$. More recently, delineating the unknown causes of how MeV may cause neurological complications like encephalitis is only just emerging. It was concluded that CD46 may be dispensable during MeV infection of neurons. Latency after MeV infection remains largely unknown within the neuronal/astrocyte synaptic cleft. However, Poelaert et al. [90] did show that astrocytes could be dependent on glutamate excitatory amino-acid transporters leading to potential MeV-induced syncytia formation.

Measles disease is frequently characterised by skin rashes employing the nectin-4 receptor ^{[5][39][91]} ^[92]. Reduction in lymphocyte counts can occur (lymphopenia) through excessive apoptosis (cell death/proliferation) in many disorders, where the regulatory homeostatic immune system is imbalanced through host cell receptor viral entry and cytokine regulation ^[92]. Chemokines affect this cellular checkpoint balancing immune cell signalling system, in an autocrine/paracrine fashion similar to hormones ^[28]. Measles virions disturb this homeostatic cellular function during natural infection. Below is a depiction of some of the intracellular proteins and pathways known to date (see Figure 4).



Figure 4. A graphical summary of the literature until 2023: Interaction of MeV or attenuated MeV with extra and intracellular proteins. IFN– α R: type I IFN receptor; IFN– γ R: type II IFN receptor; IFN– λ R: type III IFN receptor; TNF: tumour necrosis factor; IL–6: interleukin 6; MyD88: myeloid differentiation primary response 88; TRIF: Toll/interleukin 1 receptor domain–containing adaptor inducing interferon– β ; TRAM: TRIF–related adaptor molecule; STAT: signal transducer and activator of transcription; TYK: tyrosine kinase; JAK: janus kinase; IRF: interferon regulatory factor; RIG–I: retinoic acid–inducible gene I; MDA5: melanoma differentiation–associated protein 5;MAVS: mitochondrial antiviral signaling protein: cGAS: cyclic GMP–AMP synthase; STING: stimulator of interferon response gene; cGAMP:cyclic guanosine monophosphate–adenosine monophosphate; ISRE: interferon stimulating response element; GAS: gamma activated sequence; ISGF3: interferon stimulating growth factor; p53: tumour suppressor gene. Viral schematic was taken from <u>https://viralzone.expasy.org/86</u>. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 4.0 unported license.

The wtMeV cellular mechanisms involved in the causation of characteristic exanthema is comparatively unknown, although it is considered that this occurs during the recovery phase with both lymphoid and myeloid cells infected with MeV ^[93]. This is then followed by epithelial cells which

express nectin-4 as well as SLAMF1 (CD150) within the vasculature potentially explaining why the skin rash appears systemic and is instigated by immune system cells ^[93].

Innate immune responses during MeV infection

The phenomenon of vaccine failure has been known for 50 years since Cherry et al. ^[94,] described MeV outbreaks between 1971 to 1973, but the reasons remain elusive ^[95]. Some years later in the late 20th century, it became evident that the wtMeV strain infected DCs, replicated and caused loss of DC allogeneic stimulation of innate and adaptive immune system T cells ^[96]. This effectively suppresses viral antigen presentation whilst spreading throughout secondary lymphoid organs and restricting the repertoire of natural antibodies produced ^[97]. Reports from Isa et al. in 2001 ^[98] documented wtMeV infection, as duration and kinetics of the immune response before and since MeV discovery remains of interest in ensuring longer–term health *in vivo*. The prominent role of other cellular receptors during MeV infection appeared in 2012 when those cells expressing DC–SIGN from both bronchoalveolar fluids (BALF), as well as LNs could transmit MeV to B cells that usually can produce antigen–specific antibodies ^{[84,][99]}.

Kinetics of the immune response indicate that during natural MeV infection, two antibody types, IgM and IgG, are synthesised around 11 days after infection, peaking at 17-24 days for IgG in non-human primates (NHP) in vivo $^{[100]}$. However, there are at least four relevant subtypes of IgG (IgG1, IgG2, IgG3, IgG4), as well as two subtypes of IgA (IgA1, IgA2), alongside IgE and IgD, with others like IgY in avian species $\frac{[28]}{2}$. Nevertheless, it was shown using immunofluorescence assays that one type of IgG (IgG1) is predominant in blood sera in individuals (n = 154) after a rash appearance. In addition, with IgG1 present, IgG2/IgG3 appear to spike at day 2-3; moreover, both IgG1 and IgG4 remain present 10-30 years after infection or immunisation (seropositivity 100% and 86%) [98]. This cellular development of antibody response, in this case, attributed the relevance of IgG2/IgG3 95.5% seropositivity to convalescence rather than memory responses [08]. Population serology studies in 2020 (n = 1092) examined nAbs present between 10 to 12 years after either infection or immunisation [101][102]. Decreases in Measles disease mortality occurred more than 30 years prior when much of this remained unknown and still does. nAbs are considered to negate the biological and infectious effects of a pathogen. It was indicated in 2020 that IgM measured was crucial in reducing host viral propagation and effecting a host immune cell response, as the second key antibody type parallel to IgG for diagnostic assays [98]. Other research investigated antibody production, to either infection or MMR immunisation (n = 88), by age range to show that IgG3 is the dominant IgG produced (63.3%) in response to MeV infection / immunisation in children age 3 or under without synthesising IgG2; additionally, IgG2 was 42.6% of the total IgG response in children over 4 rising to 62% in convalescent adults ^[103]. During natural MeV infection, IgG1 and IgG3, are considered to be the dominant earlier humoral antibodies produced ^[103]. These remain key observations because, *in vivo*, in mice rather than humans, three subtypes of IgG2 exist ^{[104][105][106]}. Indeed in 2019, monomeric human IgG2 was described as having less effector function, but still therapeutically relevant through FcγRII (CD32) and FcγRIII (CD16), effecting microbial pathogen clearance through antibody– dependent cell cytotoxicity (ADCC) which utilises both M ϕ and neutrophil function ^[107].

During a 10–year study following MeV, as well as MuV antigens evoking nAbs after immunisation with MMR (n = 98), comparisons were made between 7 to 17 years post–immunisation of individuals. This data did not indicate a statistical difference between the production of either nAbs to Mev or MuV; but did indicate that 42% of individuals experienced more than 20% waning of MeV antibody titres with an established antibody correlate (120 milli–international units per millilitre, mIU/mL) ^[108]. Furthermore waning of IgG antibodies occurred specifically against MuV rather than nAbs against MeV ^[108]. Further to this in 2019, scientists from Boston in a crucial study during natural MeV infection of un–immunised individuals (n = 77), further clarity came through serological analysis ^[109]. It was found that the host antibody repertoire produced could be quantified with up to 73% reduction during natural MeV infection in infants ^[109]. During this study, parents graded disease severity as 44% in acute and 56% in severe MeV infection ^[109]. This change instigated by MeV infection may alter the human host immune response to other pathogens including Human Herpes virus (HHV) as well as Papillomaviruses amongst other bacterial infections (e.g., *Streptococci*) for up to 5 months after natural MeV infection with much still unknown ^[109].

Recently between 2017 to 2021, circulating B3/D8 MeV genotypes were examined during an outbreak in Italy by Bianchi et al. ^[4,9] who confirmed B3/D8 MeV genotypes to show that breakthrough infections could also occur in immunised individuals (n = 864). Specifically, they estimated <2.6% of individuals were non–responsive to MMR immunisation as measured by antibody production ^[4,9]. The significance of this remains unknown to now.

During MeV infection, it was similarly observed that B memory (B_{MEM}) cells were reduced, which would usually develop and stimulate other cells to form antibody–secreting cells (ASCs). Together

with B_{MEM} cell count reduction, an accompanying reduction in antibody secretion of two predominant types within serum and mucosal compartments (IgG/IgA) was observed, although increases in other B cells, transitional B cells, occurred being bone marrow resident B cells [110]. MeV therefore has been confirmed to selectively deplete and affect naïve B cell development with signalling pathways largely unknown, but potentially affecting the adaptive immune response during pathology ^[110]. During the acute phase of MeV infection, circulating B cells as well as T cells are infected through MeV differential affinity to CD46 and other cell receptors. CD46 receptors are present throughout the lymphoid tissues, germinal centres (GCs) and dLNs. On another note, MeV infection is associated with a robust immune response through the attenuated MMR immunisation, but infection points to a temporal lack of memory to B and / or T cell response but the level of this remains obscure. Many factors affect the rate of antibody generation and persistence, but memory T cell responses play a crucial role.

Since MeV immunisation began, technological evolution and genetic sequencing have discovered other protein factors in the immune system. These include type I interferon (IFN), type II IFN or type III IFN discovered between 1957 to 2003, besides a host of Pattern Recognition Receptors (PRR), for example, TLRs, as well as interleukin (IL) cytokines. These can modulate the immune cell phenotype in responding to infection.

To this effect in 2011, the reasons for differential antibody production were observed in MMR– immunised subjects (n = 454), with variations observed in TLR2 associated with increases in antibody production, whilst in contrast TLR4 which was associated with less antibody production within this study [111]. Authors attributed this to an innate immune regulatory gene (mitogen–activated protein kinase kinase kinase 7, *MAP3K7*), which can mediate cell signal transduction through a transforming growth factor (TGF– β), evenly expressed throughout the immune system leukocytes essential for normal cell function [111][112][113]. In 2012, further studies examined CD46 receptor single nucleotide polymorphisms (SNP) genotyped in children (n = 137) to show significant correlation could occur with MeV–specific IgG concentrations with a specific CD46 genotype (rs7144), seemingly affecting both B cells and T cells [114]. In the aforementioned study, MeV antibody titers below 324 mIU/ml were considered seronegative of which 10.2% of individuals did not produce antibodies [114]. Whilst during 2020, an Australian retrospective report investigating MeV infection (n = 297) spanned 2008 to 2017, it was outlined that sometimes primary and secondary MeV vaccine failure could potentially be observed [115]. Antibody responses could still be present and were classified as nonimmune $(IgM^{+/-}/IgG^{-})$, indeterminate (IgM^{+}/IgG^{+}) , but also waning immunity (IgM^{-}/IgG^{+}) , further elucidating potential usefulness as indicators $\frac{[115]}{2}$.

Little was known of antibody seroprevalence to MeV in individuals with cancer, until two studies of individuals (n = 959) with solid malignancies and haematologic malignant neoplasms were published in 2021 ^[116]. It was shown that 25 % of individuals in these groups lacked antibodies for MeV, whilst 38% lacked antibodies against MuV. Variable seroprevalence was noted with age groups characterised by higher seroprevalence in increasing age ^[116]. Concurrently recipients of haemopoietic stem cell (HSPC) transplants also possess significantly fewer nAbs against both MeV and MuV. Whilst in other paediatric cancer cohorts it was also noted that protective antibody titers were also reduced more significantly in acute lymphoblastic leukaemia (ALL) patients, but similarly MuV antibody waning was further noted ^[117].

Regarding the cellular mechanisms MeV utilises to disrupt cellular homeostasis, as early as 2005, observations noted that MeV was causal in inhibiting the production of a required homeostatic type I IFN a/β cytokine ^[118]. Furthermore, in 2011 in 1–year–old infants, DC–SIGN and SLAM SNPs were compared through genotyping to find type II IFN– γ responses required also varied in conjunction with antibody IgG levels ^[119]. More recently, MeV was also shown to inhibit two PRRs, TLR7 and TLR9, usually expressed within the plasmacytoid DC (pDC) lineages commonly producing type I IFN whilst presenting viral antigens required for B cell development in GCs ^[120]. This was emphasised in NHP, where cellular stimulation using combined TLR3/TLR9 agonists with an MCV that was seen to induce high concentrations of IFN synthesis *in vivo* as well as cytokines like IL–10 ^[121]. TLR9 particularly is known to be expressed by B cells and pDCs and is a factor in other skin disorders like systemic lupus erythematosus (SLE) ^[113]. With regards to the MeV–induced downregulation of type I IFN production by DCs. In 2014, Mesman et al. ^[122] did show *in vitro* DC–SIGN could inhibit cellular phosphatase activity regulating RIG–I as well MDA–5. In effect, DC–SIGN is required by MeV for cellular infection, as well as early MeV transcription and replication and suppresses DC type I IFN production affecting the the adaptive immune system response as discussed below ^[122].

Chemokine and cytokine expression during MeV infection

Chemokine research evolved since 2011, with investigations into the role of CXCL12 beginning, and being considered to be affected during MeV infection that may potentially affect APCs. It was postulated that the Runt-related transcription factor 3 (*RUNX3*) gene was a regulatory transcription factor that could regulate and maintain both T cell and monocyte receptor (CD4/CD14) expression affecting monocyte differentiation with individual angiogenic and immunosuppressive activity ^[28] [123][124]. CXCL12 is known as a B cell developmental growth factor (GF) also called stromal-derived factor 1 α (SDF-1 α). This homeostatic chemokine is ubiquitously expressed throughout the human body.

Further reports from 2016, using unbiased mRNA-sequencing technology, confirmed that immunisation against MeV elicited the production through cellular mRNA of CXCL12, together with the expression of one cell receptor, CD93, and one cytokine, IL-6 [125]. Chemokine further characterisation largely occurred in the 21st century. As mentioned, CXCL12 protein synthesis was observed to be downregulated during MeV infection $\frac{[126]}{2}$. Therefore, it is plausible that this represents a key pathway with which MeV infection can alter both monocyte lineages as well as T cell phenotypes during disease. Interestingly, CD93 is a C-type lectin transmembrane receptor affecting cell adhesion and phagocytosis by APCs. In addition, CD93 appears to have a central checkpoint function discovered, with a negative correlation to type I helper T cells (T_H1), NK cells, but also myeloid-derived suppressor cells (MDSC) in cancer as well as follicular helper T cells $(T_{FH})^{\frac{127}{2}}$. It was furthermore considered that blockade of CD93 could sensitise tumours to immune-checkpoint therapy [127]. Whereas, IL-6 in immune responses is a well-characterised cytokine, performing a role as a chemoattractant for neutrophils during pro-inflammatory immune responses; while CD93 is found expressed by cell lineages including myeloid cells, HSPCs, NK cells and platelets concurrently with neuronal, microglial and ECs $\frac{128}{2}$. It was further clarified that IL-2 along with TNF- α , and type II interferon (IFN- γ) are required for effective innate host responses during MeV infection [127]. Previous articles indicate that increases in levels of the soluble IL-2 receptor (IL2R also known as CD25), a membrane-shed marker of T_{REG} cells discovered in the 21st century can occur. [127]. Furthermore, this was accompanied by cyclical IL-17 changes produced by $T_{\rm H}$ 17 cells and other cells [127]. This is unsurprising, and the cytokine TNF- α is not only expressed within epithelial cellular layers during infection, but also during premalignant oncological conditions, where epithelial layer differentiation can be affected during inflammatory responses [129][130].

Development in 2020 indicated a second chemokine, CXCL10, was observed in serum concentrations and could be a correlate of severity during MeV infection ^[131]. These were interesting observations,

because the receptor for CXCL10 is CXCR3 expressed on many immune cells, including DCs, required for antigen presentation. More recently it was observed that MeV infects cytokeratin–positive epithelial cells in bronchial and appendix epithelia, accompanied by disruption of alveolar and bronchial epithelial cells as well as multinucleated cells expressing CD11c, characteristic of the DC or M¢ cell phenotypes expressing CD68 ^[132]. Below is depicted the cytokine and chemokine roles in the immune system as discussed below (see Figure 5).



Figure 5. A depiction of the role of CXCL12 and IL-6 in MeV infection with adaptive immune cells defined by CD molecules during MeV infection; MAIT: mucosal-associated invariant T cells. T_{EM}: effector memory T cells; T_{CM}: central memory T cell; T_C: cytotoxic T cells. Viral schematic was taken from <u>https://viralzone.expasy.org/86</u>, adapted from ViralZone, SIB Swiss Institute of Bioinformatics. The Figure was partly created with Servier Medical Art (<u>https://smart.servier.com/</u>), licensed under a Creative Commons Attribution 4.0 Unported license. Further details remain to be explored in conjunction with the role of TLRs. Since 2006, p38 mitogen– activated protein kinases (MAPK) and the role of TLR2 were determined to affect host cell responses and proliferation $\frac{1113}{1331}$. During 2019, it was however indicated that a highly conserved nuclear protein like WD repeat–containing **protein** (WDR5) could regulate MeV N and P proteins instigating viral IB growth $\frac{11341}{1341}$. Subsequently, in 2021, TLR2 SNPs during MeV infection in individuals (*n* = 100) suggest certain host genetic mutations (rs3804100) may affect cell signal transduction and susceptibility within the respiratory tract upon MeV infection $\frac{11351}{1351}$.

In 2003, when type III IFN was discovered, it was implicated that the MeV C protein may suppress type I IFN (IFN– α or IFN– β) ^[136]. The resultant inhibition by MeV infection of the JAK1 enzyme crucial to nuclear IFN signal transduction, in effect may temporarily modulate the type I IFN response, altering type I IFN synthesis with research continuing ^[137]. More recently, since type III IFN discovery, from 2015, it could be observed *in vivo* that this lack of IFN response was also accompanied by a lack of type III IFN response and measured by lack of specific mRNA gene transcripts (*MX/ISG56*) usually leading to lack of translation of type I/III IFN protein expression, a known epithelial layer expressed IFN ^[138]. More recent discoveries from 2021 show MeV can modulate mitochondrial DNA (mtDNA) in common with both +ssRNA and –ssRNA viruses by affecting the cyclic GMP–AMP synthase (cGAS) pathway affecting each of the type I/II/III IFN secretion pathways required for immune responses ^{[26][66,][139]}. Therefore MeV could modulate the homeostatic IFN systemic response essential to antiviral innate/adaptive cellular reactions. Investigations by Clifford et al. ^[140] examined the TLR role within individual infants (*n* = 238) who received MMR, but also then contracted MeV. It was then shown that that *TLR7* SNPs did not affect functional response to infection and immunisation.

Adaptive immune cell responses during MeV infection

Atabani et al., in 2001 ^[96] confirmed that natural MeV infection could dampen IL–12 cytokine production in DCs, whilst other researchers reported in 2012 additional suppressive effects on both innate B and T cells to conclude that three crucial immune cell phenotypes could be infected by MeV ^{[96][100]}. The effector host cell response to MeV infection requires these three. The adhesive nature of MeV to DC–SIGN on DCs in epithelial cellular layers is implicated as one route of affecting MeV cell infection, with other lymphocytes expressing CD150 present mainly in lymphoid tissues ^[78]. Furthermore, MeV transmission between T cells from cells expressing CD150 indicated that virological

synapses could be formed where viral proteins accumulated. This could occur through activation of DC–SIGN and was investigated together with leukocyte functional antigen (LFA–1) as well as a non–glycosylated tetraspanin (CD81) ^[14,1]. These were notable findings as LFA–1 is abundantly expressed by leukocytes and required by T cells as a motility factor utilising intercellular adhesion molecules (ICAM) within epithelial and EC layers ^[14,1]. For example, T_{EM} cells, but also recall of other T_H cells, as well as T_C cell responses across membrane barriers is required to provide longer–term adaptive immunity. Other T cells include and are defined phenotypically as above naïve T cells, together with T_{REG} cells, whilst other T_H 17 cells secrete chemical cytokines like IL–17 amongst other T cell phenotypes ^[28].

T cells can be infected through MeV F proteins binding to the PM surrounded by receptors described above. The T cell phenotypes affected include memory T lymphocytes (T_{MEM}) lacking expression of receptor proteins, like the leukocyte common antigen, CD45 (denoted as CD45RA⁻), or expressing others usual by memory T cells (denoted as CD45RO⁺) ^[100]. These specific T cells traverse and diffuse through EC layers, as well as within lymphoid tissues (bone marrow/thymus) and dLNs, utilising leukocyte–specific adhesion molecules like CD62 ligands (CD62L). It was noted that two classes of T cells were preferentially infected namely T_{EM} cells, as well as T_{CM} cells, leading to the hypothesis that natural MeV infection provokes immune cell temporal amnesia ^{[28][100]}. However, other innate immune cells developing into B cells were observed as proliferating within LNs (follicular B cells), measured by antigen kiel 67 (ki67), a cellular proliferation marker. Suggestions were that apoptosis did not occur as measured by caspase–3 expression within T cells, but rather that MeV–infected cells were preferentially depleted by T_C cells usually producing an array of effector enzymes like perforins and granzymes ^{[28][100]}.

Immunisation against MeV traditionally occurs in two doses in infants providing a prophylactic benefit by training the immune system to recognise attenuated MeV epitopes presented to T cells. The rationale of this is as described with attenuated MeV through immunisation resulting in cell–derived processed epitopes being presented to the immune cell phenotypes expressing CD46 and therefore metabolised efficiently upon stimulation ^[10,9]. Recent diagnostics commonly used up to 5 days after infection are real–time polymerase chain reactions (rtPCR); whilst serology assays have been reviewed elsewhere for MeV indicative of the sensitivity of 90.6% but also 100% specificity to date that are screened for viral variations ^[16,2].

More recent research on MeV infection (n = 26) are connotative of other T cell phenotypes affected. These comprise of T_{FH} cells alongside at least four other key T cell phenotypes being T helper (T_{H1} and T_{H2}), as well as T_{REGS} , with T_{H17} cell reduction occurring [143]. However, this involves the APCs processing antigens requiring GFs like IL-4 and IL-13, to effect functional T-cell responses. To this effect, scientists in 2017 researched these potential factors including SNPs in the IL-4 cytokine pathway in individuals (n = 137) [144]. Specifically, one polymorphism (S503P) was documented within the corresponding IL-4 receptor subunit (IL-4Ra) that could affect immunisation responses [144]. How polymorphisms affect a response to infection or immunisation remains unknown, but it is known that APCs utilise IL-4 signalling to effect APC growth, thereby facilitating presentation of viral antigens and effecting host production of IgG antibody subtypes [144]. However, in 2020, the role of T_{FH} cells was further clarified in acute MeV infection. It was then seen that signalling through the expression of the inducible T cell costimulator (ICOS, CD278) was activated together with the expression of CXCR5 with two cytokines (IL-6 and IL-21) observed in individuals (n = 42) with MeV– specific serum IgM antibodies [145].

Comparatively less is known about the role of NK cells during MeV infection or other immune cell phenotypes. However, since 1954 MeV isolation, many of the T cell phenotypes are now defined by membrane expression of both chemokine receptors and respective ligands accompanied by either membrane or soluble CD protein expression by T cells. These are commonly denoted by the leukocyte common antigen (CD45), together with CCR7, frequently expressed by migratory T_N cells. The phenotypes specifically observed to be infected in NHP during MeV infection were T_{CM} cells (CD45RA⁻CCR7⁺), or T_{EM} cells (CD45RA⁻CCR7⁻) with both expressing SLAMF1 [100][146]. Similarly, MeV is known to infect narve B cells (IgD⁺CD27⁻), as well as B_{MEM} cells (IgD⁻CD27⁺), as well as other B cells that all express a B–lymphocyte antigen (CD20⁺), but also the dominant antigen–presenting receptor, the type MHC class II receptor (HLA–DR) usually presenting 9-30aa of pathogen degraded cellular processed peptides as a ligand for TCR recognition [100][146]. In 2017, the T cell response was further analysed indicative of CD4⁺ T cells producing type II IFN– γ during the MeV infection rash period along with cytokines required for M ϕ maturation into either M1 ϕ /M2 ϕ phenotypes (e.g., IL–4, IL–10 and IL–13) [147]; just as antibody production occurring in a T_H1 type response is considered to be beneficial. However, other cytokines like IL–17 were synthesised and secreted up to 126 days after

infection, although the other 2 key types of T cells (T_{REG} and T_{H} 17 cells) roles have not as yet been measured [147].

Both of the two cell types expressed a retinoic acid nuclear receptor (ROR_Yt); furthermore, both were shortly after described to be specific for the MeV H and N proteins $\frac{[148]}{N}$. As recently as 2021, other emerging reports further confirm that MeV infects lately characterised MAIT cells expressing CD3⁺ with MHC class I–related gene protein (MR1), along with invariant NK (iNKT) cells, denoted by CD3⁺CD1d⁺ $\frac{[149][150]}{N}$. These were crucial because the MR1 protein can bind to vitamin metabolites such as those produced during riboflavin synthesis (e.g. vitamin B2) or during bacterial infection with others obscure $\frac{[151][152][153][154]}{N}$. Other T cell phenotypes are defined that include $\gamma\delta$ T cells that are also a factor which include the V γ 9V δ 2 T cell phenotypes in the developmental immune response $\frac{[155]}{N}$. To this effect, However, 2024 reports are only just clarifying (n = 38) some. It is now clarified that no significant difference occurred in cytokine production by monocytes after MMR immunisation; however, a metabolic shift may occur in $\gamma\delta$ T cells. Specifically, the dominant peripheral blood V δ 2 T cells are increased, whilst being able to produce both TNF as well as type II IFN– γ necessary for T cell activation and proliferation to infection $\frac{[156]}{N}$. Subsequent re–stimulation of CD3/CD28 V δ 2 T cells was further seen to be able to induce mitochondrial metabolic changes $\frac{[156]}{N}$.

While infectious MeV can be cleared, in 2017 it was evidenced that MeV RNA persists in peripheral blood mononuclear cells (PBMCs), together with secretions for months after ^[157]. This was observed in NHP between 84 to 140 days after infection through type II IFN– γ release required to clear viral infections ^[157]. T_H cells expressing CD4 were observed as crucial early in infection. The T_H cells expressing CD4 were active earlier in infection and appeared polyspecific later during infection against MeV H and N expressed proteins ^[157]. This was accompanied by an increase of CD4⁺ T cells secreting IL–17 (1.35–2.27%) that were MeV H protein–specific ^[157]. However, T_C cells were still active at 113 days after infection indicative that immune responses are still sensing MeV–presented epitopes ^[157]. The T_C cell response therefore does continue to occur. In 2018, Arbore et al ^[158] examined CD46 deficiency to note the optimal type II IFN– γ response and resulting cytotoxicity was dependent on both CD46 and T_C cells. Notably CD46 stimulation was indicated to be a stronger checkpoint than CD28 on T cell phenotypes (expressing CD4/CD8). This could occur with the upregulation of CD107a, and increased activity of the serine protease granzyme B effecting the apoptotic function in a perforin–dependent pro–apoptotic manner. It was also shown then that the

inflammasome NLRP3 (nucleotide oligomerization domain, **leucine**–**rich repeat**, and pyrin domain– containing protein 3) sensing of microbial pathogens could be independent of MeV infection ^[158]. Notably, it was then observed that this CD46 receptor could be co–stimulatory and reflect divergence through metabolic pathways whilst directing an optimal T_{H1} response. However, stimulating complement (C5a) production could regulate optimal CD8⁺ T cell responses through receptors (C5AR1 and C5AR2 expressed by T cells ^[158].

To this effect, however, 2024 reports are only just emerging of the role that MMR vaccination has on other immune cell phenotypes. It has now been resolved that no significant difference occurred in cytokine production by monocytes after MMR immunisation; however, a metabolic shift may occur in $\gamma\delta$ T cells, with the dominant V δ 2T cells overall percentage increasing and being able to produce both TNF as well as type II IFN– γ (n = 38) ^[159]. Subsequent re–stimulation of CD3/CD28 V δ 2 T cells was seen to be able to induce cellular mitochondrial metabolic changes ^[159].

Limitations

Above some of the research will have included *in vivo / in vitro* studies subject to guidelines. Immunisation is subject to both regulatory as well as local authority jurisdiction for further guidance and is dependent on supply chains as well as ongoing diagnostic tool development discussed elsewhere (see Supplementary materials). Safety monitoring of immunisation occurs and is of consideration but discussed elsewhere, whilst similarly, vaccine efficacy remains difficult to quantify during MeV–caused disease ^{[160][161]}. New vaccines remain in development ^[162]. LAVs are subject to clinical guidance; specifically for individuals with diagnosed immunodeficiency (e.g. Severe Combined Immunodeficiency, SCID), or immunosuppressed (e.g during acute or chronic leukaemia/lymphoma treatment) (see Supplementary Materials). Similarly

Discussion

In recent years, the European Centre for Disease Control and Prevention (ECDC) surveillance reports up to 2023 indicate the incidence of MeV detected cases between 2018 and 2019 (34.4 and 27.2 per million population) has decreased in 2023 to 5.2 cases per million population, without attributable fatality caused by MeV (see Supplementary materials). The most recent mortality data in 2018 characteristic of overall MeV–caused disease fatality globally illustrates around 140,000 individuals remain affected predominantly under the age of 5 and also immunocompromised individuals ^[5]. This is affected by vaccine hesitancy, but also by implementing immunisation programmes and schedules through cooperation globally $\frac{[163][164]}{2}$. It is considered that immunisation coverage exceeding 90% or 95% could potentially lead to the near eradication of MeV similar to other viruses like VARV long since extinct [164]. Recent reports indicate that 86% of MeV-diagnosed cases occurred in un-immunised individuals, with 66% of cases in un–immunised adults. This occurred in countries where the range of two doses of MCV uptake varied between 71% to 99% (see Supplementary materials). Such figures are notable. Sporadic MeV cases can occur as the immune response and resulting rates of Measles disease prevalence could be affected by a myriad of factors as well as immunisation evoking immune system responses. It is currently indicated that serious complications of Measles disease can be acute encephalitis and sclerosing panencephalitis occurring 7-10 years after initial MeV infection ^[5]. Nevertheless, the longevity of immunological responses to the attenuated MeV, since MCV or MMR immunisation inception remains unknown. Yet there has been a reduction in overall MeV disease case counts and disease burden since the progressive introduction of immunisation $\frac{[165][166]}{[166]}$. Given high seroconversion rates observed after MMR immunisation, it could be considered that vaccines targeting MeV may yet lead to eradication, although unknown genetic factors can affect the immune response [164]

In 2024, Differential MeV–induced antibody profiles were examined in China (n = 2629) recently [167]. These were denotative of a potential antibody threshold at around 14.3 years of age with antibody concentrations around 200 mIU/ml suggesting waning immunity contrary to previous indicators [167]. However, T–cell responses vary during development adding to the complexities [168]. The arbitrary scale of antibody responses is being compared globally, with reagents used determined by the specificity and sensitivity of the mAb [27]. Timing of immunisation is indicated that could affect the nAb response against MeV usually occurring in infants [169].

Whilst CD150 was confirmed as a key MeV cellular entry receptor before 2018, it was noted that MeV infects T_N cells and B_{MEM} cells, as well as both DCs, M1 ϕ /M2 ϕ , but not the other key APCs that are monocytes *in vivo*. Research opinions vary on whether MeV infects monocytes, however, historically this was observed in 1975 research ^{[170][171]}. The wtMeV may appear causal in the cytotoxic activity of lymphocytes entering B cell follicles between acute to severe MeV infection ^[143]. Seemingly, MeV immunosuppression has utility beyond what was originally known, with the role of T_{REG} cells and NK

cells remaining mostly in the dark. However, Griffin et al. in 1990 $^{[172]}$ examined NK cell responses which did appear unresponsive but could be rescued *in vitro* by the DC maturation/stimulation cytokine IL-12. Cytolytic activity of *Paramyxoviridae* is known in similar viruses of this family like NiV $^{[16]}$.

Other factors largely unknown that MeV affects during disease were noted in 2011, when a systematic review examined synthetic vitamin A supplementation in infants aged 6 months to 5 years as reducing overall mortality by up to 30% [173]. Vitamin A effects on the immune system phenotypes remain comparatively unknown, as the discovery of the relevant stimulated by retinoic acid 6 (STRA6) protein receptor occurred in 2013, remaining central to vitamin A metabolism [153]. Furthermore in France during 2017, a trace element, selenium (n = 94), was found to be reduced in the sera of individuals with acute MeV-caused disease $\frac{174}{175}$. These were interesting findings because selenium is considered to be essential to human health [175][176]. Other recent studies before and since the recent COVID-19 pandemic are indicative that CD150 has a role in DC maturation. Since other DC phenotypes were observed between 2006 to 2018 and specifically in 2017, further developments will be interesting to see [133][177][178]. Current knowledge indicates that the SNPs within the predominant host CD46 receptor were only observed from 2012, at least with attenuated MeV strains, where CD46 was highly expressed on monocytes; but also a specific CD46 genotype (7144CC) may affect CD46 cellular function and resultant activation as well as the host response to MeV immunisation [114,][179]. Furthermore, many unknowns remain regarding SNPs of the TLRs also affecting a host immune response. The role of type III IFN in MeV infection remains elusive as other gene or protein deficiencies may occur that affect host viral and bacterial immune responses during development and throughout life [180].

Overall longer-term autoregressive models conducted by Pezzotti et al. ^[126] of immunisation against 10 vaccine-preventable diseases over 115 years (spanning 1900 to 2015) indicate that immunisation can effectively reduce disease ^[126]. To this effect, it is now indicated in long-term studies that vaccine reduction of infections causing disease occurs in the order of diphtheria, MuV, VZV, and then MeV ^[126]. However, guidelines illustrate that there remain many unknowns. For example, the usage of LAVs, as in MMR, in specific individuals with diagnosed primary or acquired immunodeficiency disorders can be contraindicated or in certain populations of immunosuppressed individuals despite the documented decline in overall infections (see Supplementary materials). To this effect the details above provide further detail. Reports remain scarce on MeV and immunodeficiency in 2024. However, it was 1952 when Bruton discovered X-linked agammaglobulinemia (XLA) that could plausibly result in humoral immune response deficiency in humans ^[181]. Some years later in 1996, Griffin et al. ^[182] to this effect continued this line of research by developing an in *vivo* research model to further examine strains of the attenuated MeV requiring further clarity.

Conclusions

The longevity of humoral/adaptive correlates to MeV infection or vaccine correlates of protection remain unknown, although longitudinal studies suggest natural infection and/or immunisation against MeV does induce high concentrations of nAbs preventative of pathogenic disease. The relevance of MeV as an infectious disease is that through nAb production to the attenuated MeV, stimulation occurs of the rate of recalled memory B and T cell responses, and a combined duration of potentially 10 years or more is likely. However different viral infections have individually different physiological and immunological responses. Measles immunisation seemingly induces a beneficial host repertoire of antibody types that stimulate immune cells to produce chemokines and cytokines reducing host chronic disease severity and/or reducing MeV cellular replication through training the immune system. This is likely to occur because of a conserved MeV H protein. Above the role of both innate and adaptive immune cells is outlined in response to MeV infection underpinning how immunisation evokes a host immune response.

At this time two MeV accessory proteins (C/V) are known that could affect the type I IFN receptor transduction STAT1/2 proteins. Innate immune responses to MeV infection may be independent of type I/III IFN synthesis with much remaining uncharted and the topic of ongoing research. Currently, 250 clinical trials investigating measles have been completed with 32 ongoing (see Supplementary materials). Beyond the outline above, comparatively much remains in the dark concerning the MeV replication mechanisms employed within cells, but is indicated by the formation of IBs [53][158][183]. Further clarity will be required as to how other T cell phenotypes are affected by MeV infection.

Despite the comparative success of immunisation against MeV to date, with lack of MeV antigenic variation, much remains obscure on a pathogen that has high transmission rates affecting predominantly infants under the age of 5. Alternatives to traditional vaccines are only now emerging, with microneedle patches (MNPs) developed soon to enter phase 3 clinical trials designed to counter MeV and RuV as alternatives to the initial MMR ^[184].MeV was initially declared eradicated in the USA (2000), but also the United Kingdom (2016) with outbreaks occurring since. More recently in 2020, a

further five countries (Bhutan, the Democratic Republic of Korea, Maldives, Sri Lanka, Timor–Leste) are now considered to be leading the way in limiting MeV transmission for more than one year with B3, D4, D8 and H1 as the reported circulating MeV genotypes prior (see Supplementary materials). Future research should therefore consider the other T cell phenotypes and transcriptome studies. It can be considered through the outline above that there are similarities with the usage of VACV which similarly induces immune responses that have led to the eradication of Smallpox disease caused by VARV through immunisation development with research ongoing ^{[4][182][185][186][187][188]}. Given these similarities, the longer–term considerations of the benefit of immunisation are outlined above in scientific terms, much of which was unknown in 1954 upon the isolation of the MeV pathogen.

Abbreviations

- APC: antigen-presenting cell
- CD4: cluster of differentiation 4
- CD46: cluster of differentiation 46
- CD93: cluster of differentiation 93
- CD150: cluster of differentiation 150
- CXCL12: chemokine ligand 12
- DC: dendritic cell
- DC-SIGN: DC-specific intercellular adhesion molecule-3-grabbing non-integrin
- EC: endothelial cell
- GF: growth factor
- IFN: interferon
- Ig: immunoglobulin
- IL: interleukin
- LAV: live attenuated virus
- LN: lymph nodes
- Mφ: macrophage cell
- MCV: measles containing vaccine
- MHC: major histocompatibility complex
- MMR: measles, mumps and rubella
- MeV: measles virus

- nAbs: neutralising antibodies
- MHC: major histocompatibility complex
- NHP: non-human primates
- NK: natural killer cell
- PM: plasma membrane
- SNP: single nucleotide polymorphism
- T_C: cytotoxic T cell
- T_{CM}: central memory T cell
- T_{FH}: follicular helper T cells
- T_H: helper T cell
- T_{REG} regulatory T cell:
- TLR: Toll-like receptor
- TNF: tumour necrosis factor
- VARV: variola virus

Supplementary Materials

- 1. WHO Measles Fact Sheet: https://www.who.int/news-room/fact-sheets/detail/measles
- 2. Measles, Mumps and Rubella (MMR): <u>https://www.who.int/teams/health-product-policy-and-</u> <u>standards/standards-and-specifications/vaccines-quality/measles-mumps-and-rubella-</u>
- 3. History of Measles vaccination: <u>https://www.who.int/news-room/spotlight/history-of-</u> <u>vaccination/history-of-measles-vaccination</u>
- 4. Diversity of wild-type MeV: Genetic diversity of wild-type MeV and the global nucleotide surveillance database (MeaNS); <u>https://www.who.int/publications-detail-redirect/WER9030</u>
- 5. MMR Vaccine: https://vaccineknowledge.ox.ac.uk/mmr-vaccine#Ingredients
- 6. Immune cell expression of SLAMF1: <u>https://www.proteinatlas.org/ENSG00000117090-</u> <u>SLAMF1/single+cell+type</u>
- 7. Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (PDB): X-ray diffraction, electron microscopy and nuclear magnetic resonance MeV protein characterisation
- 8. Immune cell expression of SLAMF1 (CD150): <u>https://www.proteinatlas.org/ENSG00000117090-</u> <u>SLAMF1/immune+cell</u>

- 9. Immune
 cell
 expression
 of
 DC-SIGN
 (CD209):

 https://www.proteinatlas.org/ENSG0000090659-CD209/immune+cell
- 10. Immune
 cell
 expression
 of
 CD209
 ligand
 (CD209L):

 https://www.proteinatlas.org/ENSG00000104938-CLEC4M/single+cell+type
- 11. CDC genetic analysis of Measles virus: <u>https://www.cdc.gov/measles/lab-tools/genetic-</u> <u>analysis.html</u>
- Measles immunisation information for public health professionals, including updates: The green book, chapter 21; <u>https://www.gov.uk/government/publications/measles-the-green-book-</u> <u>chapter-21</u>
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- 16. Measles European Centre for Disease Control (ECDC) Annual Epidemiological Report for 2023: <u>https://www.ecdc.europa.eu/en/publications-data/measles-annual-epidemiological-report-</u> <u>2023</u>
- 17. Measles Elimination in the USA CDC report: https://www.cdc.gov/measles/elimination.html
- 18. Measles cases deposited to the global health repository (WHO): <u>https://www.who.int/data/gho/data/indicators/indicator-details/GHO/measles---number-of-</u> <u>reported-cases</u>
- 19. Measles Complications (CDC): https://www.cdc.gov/measles/symptoms/complications.html
- 20. Measles and Rubella Laboratory Network: <u>https://www.who.int/europe/initiatives/measles-and-</u> <u>rubella-laboratory-network</u> Measles and Rubella Laboratory Network (who.int);
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- 23. CDC Measles outbreaks 2024: <u>https://www.cdc.gov/globalhealth/measles/data/global-measles-</u> outbreaks.html
- 24. Annual Status Update on Measles and Rubella Elimination Germany 2022 report: <u>https://www.rki.de/DE/Content/Kommissionen/NAVKO/Berichte/Bericht_2022_en.pdf?</u> <u>_____blob=publicationFile</u>
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Statements and Declarations

Author contributions

BB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing–original draft, review & editing, Validation, Visualization. **IF**: Data curation, Formal analysis, Investigation, Methodology, Writing–review & editing, Resources, Visualization, Software, Supervision. **CI**: Data curation, Formal analysis, Methodology, Investigation, Writing–review & editing, Software. **JS**: Writing–review & editing, Software. **ECC**: Data curation, Formal analysis, Investigation, Methodology, Writing–review & editing, Software, Supervision.

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Consent to participate

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Ethical approval

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Availability of data and materials

Requests for accessing the datasets could be directed to the corresponding author (<u>info@biochem123.org</u>) or Supplementary materials.

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