[Short Communication] Immunology of a Morbillivirus: Measles 1954 to 2023

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Abstract

Measles is a virus, abbreviated to MeV, thought to have existed around 4000 years ago affecting predominantly infants but also immunocompromised individuals and others remaining a public health issue. The causal virion is defined biologically within the Family *Paramyxoviridae*, Genus *Morbillivirus* and Species *MeaslesMorbillivirus.* Similar to other infections, MeV is an airborne infection with the virion composed of an RNA genome code encoding for eight predominant proteins. The first isolation of MeV occurred in 1954 known as the “Edmonston strain” from David Edmonston, a student at Fay School in Boston. The lack of antigenic variation by the MeV particle discovered since is suggestive that the third pathogen with the potential to be eradicated requires further research. In 1954 knowledge of the immune system had only just started emerging. Immune cells traverse barriers known as the glycocalyx and endothelial surface layer (GC-ESL) requiring stimulation to restrict viral replication through antigenic challenge in the respiratory epithelial and endothelial cell layers. Immune cells have different phenotypes and regulate infection through inhibitory and stimulatory proteins like cytokines, and chemokines as well as adhesion molecules and receptors transversing permeable organ tissues from the lymphoid system. Here is a discussion of contextual MeV innate and adaptive immune responses to infection or immunisation. Potential explanations to elucidate this further with regard to past, present, and future research are considered. This outline will provide key insights and be useful to researchers, clinicians and academics in the future.

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Introduction

Comparatively less is known about the immunology of MeV natural innate and adaptive immune responses as Information Technology (IT) did not exist in 1954 whilst biological research developed. Immunisation has been utilised largely since 1971 predominantly utilising a weakened or “attenuated” MeV strain, but also a formalin-inactivated vaccine [1]. Just prior, in 1948, a pioneer Mark Adams examined how 7 bacterial viruses could be inactivated through gas/liquid exchange through bubbling nitrogen over *Escherichia coli.* Therefore it was then observed that a preventative chemical could inactivate pathogenic infection. As early as 1965 it was indicated that MeV could be eradicated [2]. A team at Boston Children's Hospital comprised of John Franklin Enders and others isolated MeV from an 11–year–old individual patient serum sample. Alongside Samuel Katz, and notably Maurice Hilleman, this led to the development of the first live attenuated vaccine (LAV) [3]. In 1971, the first trivalent mumps, measles and rubella (MMR) vaccine was licensed for use in the United States of America (USA) [3]. Shortly after in 1980, the eradication of Smallpox disease caused by the Variola virus (VARV) was confirmed by the World Health Organisation (WHO), which was the predominant debilitating pathogen of the 20th century [4]. Measles was then considered to be causal of more than 2 million deaths each year (See Supplementary Materials). However, in 2018 MeV mortality remained estimated at around 140,000 annually with variable infection/mortality rates globally and in resource-limited countries with environmental factors also contributing to the decrease of severity of MeV infection besides immunization (See Supplementary Materials) [5]. Around 1981, as research evolved, Bellini et al published an article discussing the immune reactivity of the purified MeV haemagglutinin (H) protein [6].

The rates of MeV infection causing disease are affected by a myriad of factors as well as immunisation with the latter considered to evoke a predominant prophylactic innate and adaptive immune system response in many populations. The Rinderpest virus (RPV), a member of the same Genus Morbillivirus as MeV, was the second reported eradicated virus in 2011 (See Supplementary Materials). However, here we discuss what is known so far as *Paramyxoviridae* (MeV), including both MeV as well as Nipah virus (NiV) are known to cause severe neurological diseases including blindness and

brain damage through unknown cellular mechanisms in a rare minority of infections [1][3][7][8][9]

Immunisation against MeV is considered to induce long–term immunity; however little is known about the underlying biological mechanisms of how this occurs during natural infection [1][10]. Two other attenuated MeV strains since the original Edmonston strain discovery, are utilised which are “Schwarz” and “Moraten”, as well as others derived since 1954[1]. The MeV virion particle is comparatively also considered to be a potential viral vector that can be engineered to target other viral pathogen antigens expressed by Human Immunodeficiency virus (HIV), Dengue Fever virus (DENV), as well as Chikungunya virus (CHIK), each in development discussed elsewhere [11][12]. Furthermore, potential applications as an oncolytic viral (OV) vector were recently examined as a potential therapeutic in 2022 in the treatment of glioblastoma [13][14][15][16]. The methodology behind this is under further development as the original attenuated vaccine-utilised strain of MeV can infect host cells expressing one receptor, the cluster of differentiation molecule (CD46), whilst the attenuated virus can induce an active immune response causal in longer–term immunogenic host responses, with similarities to the Vaccina virus (VACV) utilised against VARV (see Supplementary Materials).

Measles virus remains apart as a pathogen from many other viral infections because of the overall R0 (transmission rate), considered to be higher than other pathogens. Accordingly, the R0 is indicated within the range 12-18 with affliction in vulnerable infant populations predominantly [17]. The efficacy and safety of MMR immunisation were the subject of debate in the early 21st century discussed elsewhere [18]. Seminal reports in late 2021 utilising population real–world data (RWD) were suggestive of the efficacy of more than 90% to either the trivalent or quadrivalent options that were manufactured and further designed to counter Varicella Zoster (VZV) virus viral antigen epitopes [1][19]. However, more recently it has been indicated that current MeV immunisation achieves nearly 98% seroconversion with antibodies generated predominantly neutralising the conserved H protein of the attenuated MeV strain [20][21][22][23][24][25]. The terminology of vaccination and immunisation are derived from VACV and VARV research with the latter causal in Smallpox disease with the former evoking active prophylactic immunological responses in a host animal or human, better characterised since discovered in 1796 [26]. 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 two types of host immune responses with the first utilised that may be long-lasting following infection or immunisation [27]. The second passive type of immunity refers to the transfer of antibody types in hosts, for example, Immunoglobulin G (IgG) or similar other licensed preparations like Rabies Immunoglobulin (RIG) or other monoclonal antibody preparations (see Supplementary materials) [28].

Different proteins utilised in research and as vectors can be a beneficial factor in the immune system program priming at least two types of immune cells to effect an immunogenic response and clear pathogens effectively [16]. Many phenotypes of immune cells are known in the 21st century [29]. Longevity and kinetics of antibody production by B cells requires T cells to adequately stimulate a recall memory immune response. Furthermore, the subtypes of B cell antibodies and T cells were further described in the 21st century alongside other T cell phenotypes [29]. Below is presented the immune cell detail known so far about immunological correlates and phenotypes that pertain to a host human response to natural MeV infection.

Structure of Measles Virus

The MeV virion particle size is 15,894 kilobases (kb) from the 3' end of the negative (-ve) sense single–stranded (ss) ribonucleic acid (RNA) genome code –ssRNA strand (see Supplementary Materials) [20]. This encodes the nucleoprotein (N), followed by a conserved haemagglutinin (H) protein fusion (F) proteins, matrix (M) proteins followed by a trimer of **phosphoproteins (P) and 2 non–structural proteins (**C/V) and then a larger polymerase (L) enzyme towards the 5' end of the RNA genome. The L protein polymerase directs and sequentially transcribes through binding to the MeV RNA at the 3' leader sequence with polyadenylation occurring during synthesis with V protein produced through RNA editing and a P protein produced from the C protein. This utilises host cellular machinery to translate amino acids (guanine, uracil, cytosine and thymidine). Viral attachment of the MeV virion particle can occur through the H protein attaching to the host cell receptor with the fusion (F) protein allowing entry through the plasma membrane (PM) where the viral mRNA is capped and polyadenylated within cellular cytoplasm [30]. Much remains unknown about how measles transverses cells and replicates intracellularly; however, in 2019, it is indicated that the MeV virion particle forms inclusion bodies (IBs) without a membrane, rich in three MeV synthesised proteins that are N, P, and L proteins [31]. In 2019 the MeV phosphoprotein is indicated to act as a chaperon and cofactor for the L protein with a multimerization domain (MD) that affects gene expression of MEV [23]. The M protein of Paramyxoviruses directs virion assembly by interacting with cell membrane phospholipids like phosphatidylserine (PS) and phosphatidylinositol 4,5–bisphosphate (PI(4,5) P_2) that could be potential therapeutic inhibition therapeutic targets facilitating the spherical or filamentous protrusions formed during viral egress [21]

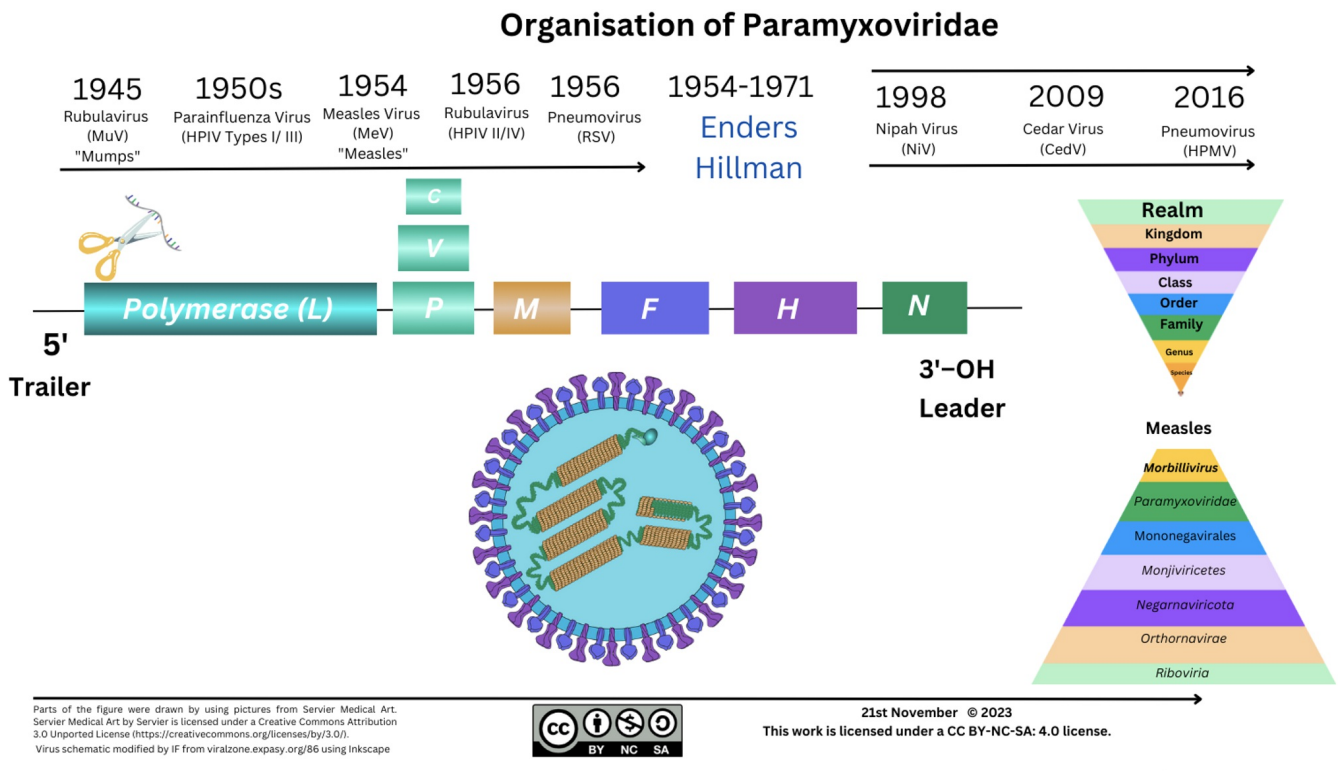

Figure 1. Structure of Measles Virus and Historical Paramyxoviridae Perspectives

History of Measles

Genetic characterisation of the MeV virus particle indicates ancestry before 1915, with extensive research indicating that the H protein was conserved explaining why current therapeutics remain relevant for the prophylaxis of MeV infection [32]. Mutation rates of the MeV particle were estimated in 1999 at 9 x 10^{-5} per base/replication with a genomic mutation rate of 1.43 per replication cycle indicating that point mutations were comparable between other –ssRNA viruses including Poliovirus but also Vesicular Stomatitis virus (VSV) [33]. 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 genotypes known sequences further designated by a number (e.g., B3, H8). It was recommended by the WHO that 450 nucleotides encoding the carboxyl (–COOH) amino–acids of the nucleocapsid (N) protein would be used to assign the genotype [34].

More recently in 2015, investigations during MeV outbreaks in Canada occurred of MeV H1 and D8 strains[35]. In 2018, the MeV genotypes in global circulation had decreased to 4. These were denoted by two MeV strains (B3/D8) together with two others (D4/H1) globally during 2020 [36]. Out of these, two (B3/D8) are known to be endemic across six of the WHO regions [37]. To this effect, continuing surveillance in Italy between 2015-2019 documented MeV genotypes (n=1273) submitted to Genbank utilising H as the genotype to identify MeV) [38]. Comparisons occurred with prior MeV genotypes to find a B3 400V clade where alanine (A) was substituted by valine (V) [38]. It was uniquely indicated that within the MeV B3 A400V clade, 62% of individuals affected by MeV had been immunised prior [38]. Furthermore, MeV D3 also had a point substitution to threonine (T) seemingly within the MeV haemagglutinating and noose epitope (HNE) [38][39]. The authors further describe epitopes in common that are targeted by the immune system including a receptor–binding epitope (RBE), a sugar–shield epitope (SEE), as well as a loop epitope (LE), and a neutralising epitope NE) [38][40]. The HNE conformation of amino–acids (379-400) 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 [38][39]. Below is shown the evolution of wild–type (WT) and attenuated MeV strains during research since 1954 isolation (See Figure 2).

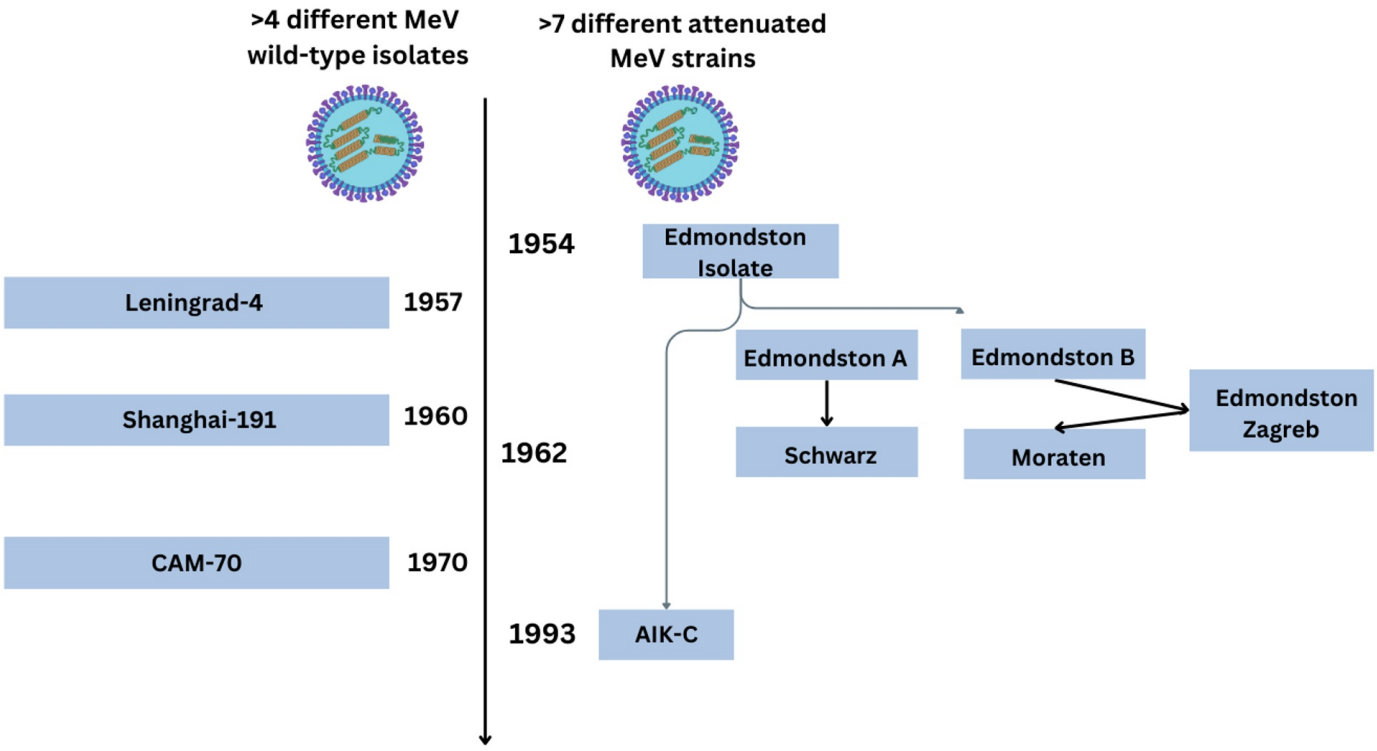

Figure 2: Evolution of 20th Century Measles Virus Strains

Development of Measles Virus Research

Many viral protein point mutations can affect immunologically programmed responses to pathogens. During 2009 as research development continued, it could be seen that the attenuated MeV particle and vaccine strains derived rather than the wild–type (WT virus) utilised one predominant receptor discovered in 1993 (CD46) [41]. It is considered that this cellular receptor is expressed by many nucleated cells [41]. Since then, protein epitope prediction and molecular mapping have remained an ongoing development for the immune system to be trained to be more effective in responding (See Supplementary Materials). During a host immune response to pathogenic antigens, fragments (epitope peptides) are presented and processed through two types of Major Histocompatibility Complex (MHC type I/II) encoded by the Human Leukocyte Antigen (HLA) utilising antigen–presenting cells (APCs). The APCs include dendritic cells (DCs), monocytes and macrophages amongst a network of better–characterised immune system cells [9][29][42]. In 2015 the antigenic stability was then further attributed to inflexible F and H proteins further indicating that MeV generates a polyclonal response predominantly against F and H proteins [22]. [43]

Measles Virus Receptor–Mediated Infection

Measles cellular infection was further researched after immunisation with the attenuated virus to occur through one receptor (CD46) [2]. In 2000, MeV eradication was indicated in the USA after 20 years and remained a target by the WHO for eradication with sporadic outbreaks occurring since (see Supplementary Materials) It is considered through research that MeV infects white blood cells (WBCs) called lymphocytes expressing a second receptor (CD150), known as a

signaling lymphocyte activation molecule family member 1 (SLAMF1) utilising nectin–4 as a host cell receptor; with these specifically expressed on certain subtypes of cells including DCs [44][45][46].

To this effect, research in Germany in 1993 by Dorig and Naniche showed that CD46 could be inhibited by two types of antibodies [41]. The two types of antibodies then were considered monoclonal and polyclonal antibodies defined by protein specificity. Therefore CD46 was considered to be an adhesive entry receptor that the MeV utilises for cellular entry across the phospholipid membrane [41]. Thereafter the first protein receptor CD46 that MeV utilised to enter the host cells was found to be activated and expressed within the myeloid cellular lineages and could also bind to complement proteins (C3b/C4b), a crucial part of coagulation system pathways. Antibodies synthesised by B cells possess two antigen binding domains that recognise pathogenic epitopes (Fab) receptors and constant (Fc) protein domains with the latter signalling to cells. These affect antibody opsonization (binding) to other cellular membrane receptors to effect an immune response through signaling and homeostatic complement regulation synthesizing fibroblast growth factors (FGF) as well as angiogenic factors contributing to vascular growth. Knowledge of this then was lesser unknown, however, the CD46 receptor utilises is indicated to be preferentially expressed during oncogenic disorders and is described as a “pathogen magnet” in differential infections [41][47]. It appears that the initial receptor, CD46, is localised with many proteins that can enhance FGF necessary for angiogenesis during common skin and systemic viral infections affecting different organ systems.

The second receptor method utilised for cellular infection, CD150 (SLAMF1), is considered to be expressed throughout the primary immune system organs (bone marrow/thymus), secondary (spleen, tonsils, lymph nodes) as well as tertiary (e.g., bronchus–associated lymphoid tissue (BALT) and by platelets and haematopoietic stem cells (HPSC) [48]. Nectin–4 (poliovirus–receptor–like 4, PVRL4) has been indicated as a third receptor of relevance during MeV infection, overexpressed in specific tumour carcinomas like breast, lung, colorectal, pancreatic, as well as ovarian cancer usually expressed at lower levels during infancy when MeV infection frequently occurs [45]. Nectin–4 clarification came as recently as 2012, similar to other types of poliovirus receptors (PVR), like CD155 [46]. These are individually considered as nectin–1 (CD111), an entry factor receptor for herpes simplex (HSV–1/HSV–2), with Nectin–2 (CD112) an entry factor of Human Herpes viruses (HHV), whilst Nectin–3 (CD113) was also characterised prior [49]. As discussed above monoclonal antibodies were shown in 2016 that can inhibit MeV cellular entry and resulting disease through binding to CD46, CD150 and nectin–4 [39].

Measles disease is frequently characterised by skin rashes utilising the nectin–4 receptor clarified since 2000[1][50][51][52]. 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 [52]. However, chemokines also affect the cellular checkpoint balancing immune cell signaling in an autocrine/paracrine fashion similar to hormones [29]. Measles virions disturb this normal homeostatic cellular function during natural infection outlined further below with much remaining unknown. Other cells that are infected include endothelial cells, but also neurons and astrocytes that can cause delayed persistent inflammation through MeV infection causing central nervous system (CNS) symptoms. In 2015 this was considered as 4 classifications, namely primary MeV

encephalitis, but also acute post–MeV encephalitis, MeV IB encephalitis, as well as subacute sclerosing panencephalitis (SSPE [24]. This is a lesser observed phenomenon but is indicated by incidence within 6.5-11 cases per 100,000 MeV infection some years after or following infant MeV infection [24]. Below is depicted some of the intracellular proteins (See Table 1 and Figure 3).

Abbreviation	Protein
ISRE	Interferon stimulating response element
ISGF3	Interferon stimulating growth factor
GAS	Gamma–activated sequence
STAT	Signal transducer and activator of transcription
TYK	Tyrosine kinase
JAK	Janus kinase
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
STING	Stimulator of interferon genes
cGAS	Cyclic GMP-AMP synthase
cGAMP	Cyclic guanosine monophosphate–adenosine monophosphate
IRF	Interferon regulatory factor 3/7/9
RIG-I	Retinoic acid-inducible gene I
MDA5	Melanoma differentiation-associated protein 5
MAV	Mitochondrial antiviral signaling

Table 1. Key to Intracellular Proteins (See Figure 3)

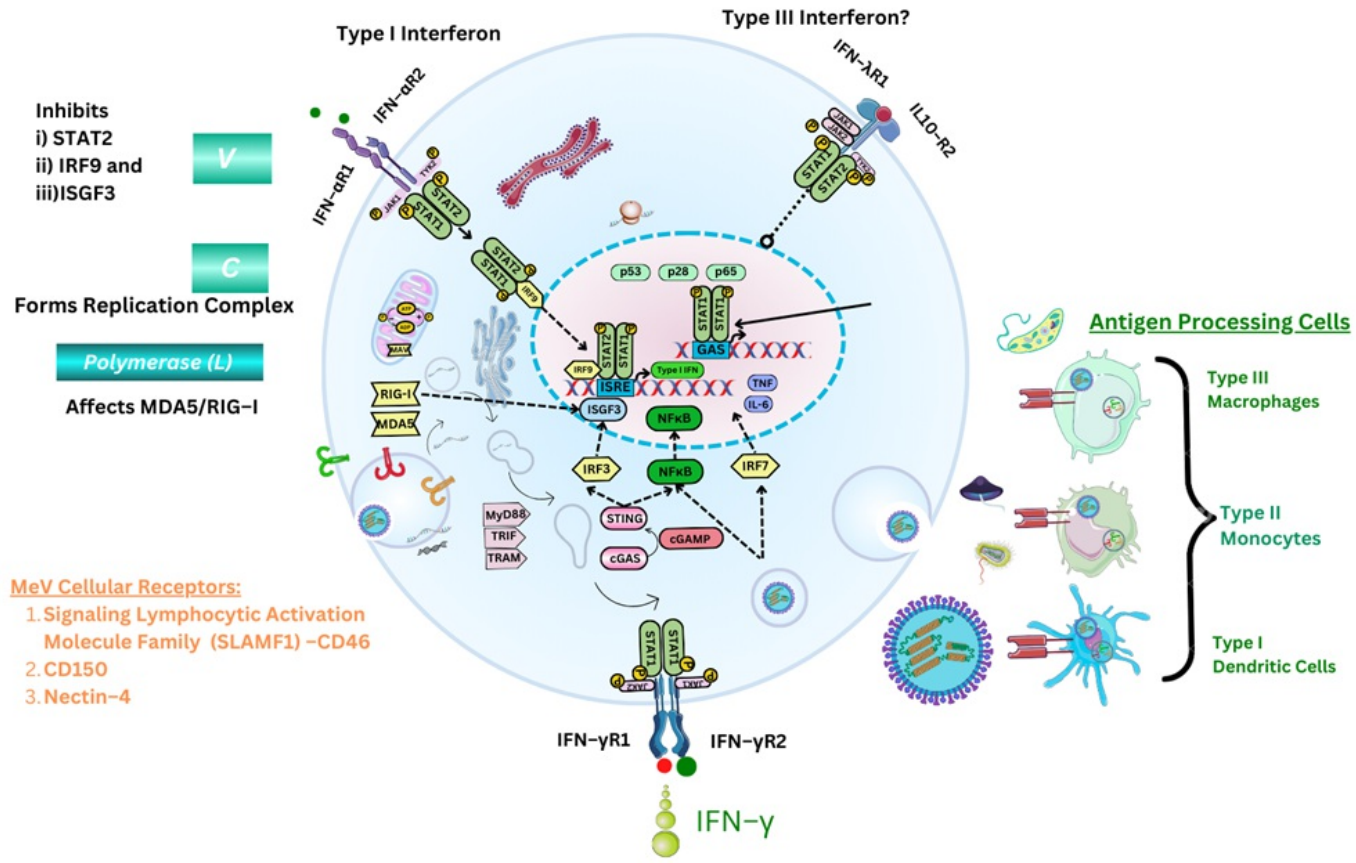

Figure 3. Evolution of 20th Century Wild Type Measles Virus and Attenuated Measles Virus Strains

Innate Immune Responses during Measles Virus Infection

The phenomenon of vaccine failure has been known for 50 years since Cherry et al. described outbreaks between 1971 and 1973 [53][54]. The reasons for this remain unknown. From 2001 reports documented examining natural MeV infection, as duration and kinetics of the immune response remain of interest [55]. Kinetics of the immune response indicates that during natural infection by MeV, two specific antibody types, defined as immunoglobulin proteins, IgM and IgG, are synthesised at 11 days after infection, peaking at 17-24 days for IgG in non–human primates (NHP) *in vivo* [56]. However, there are at least 4 relevant subtypes of IgG (IgG1, IgG2, IgG3, IgG4) as well as 2 subtypes of IgA (IgA1, IgA2) alongside IgE and IgD with others like IgY in avian species.

Nevertheless, it was then shown that one type of IgG (IgG1) is predominant in blood sera early after MeV infection, whilst IgG2/IgG3 appear at cyclical levels with the cellular memory response developing alongside switching between antibody types documented largely after this, with IgG4 appearing later after MeV infection [55]. Population serology studies in 2020 (n=1092) examined neutralising antibodies (nAbs) between 10-12 years after either infection or immunisation against MeV [57][58]. Decreases in measles mortality occurred over 30 years prior when much of this remained unknown and still does. Neutralising antibodies **as the name suggests are considered to neutralise the biological and infectious effect of a pathogen. It** was indicated that the other antibody type (IgM) detected was considered crucial in reducing host viral

propagation, host immune response, and time of sample collection as well as being the second key antibody type alongside IgG for diagnostic assays [55].

Other research indicates 4 years after MeV infection that IgG2 and an unknown antibody subtype of IgG2 were relevant during convalescence [59]. During natural MeV infection, IgG1 and IgG3, remain the dominant earlier humoral antibodies produced [59]. These were interesting observations because, *in vivo,* in mice rather than humans, there are observed to be a further 3 subtypes of IgG2 [60][61][62]. Many factors affect the rate of antibody generation and persistence, but also memory T cell responses play a role in influencing the innate immune system. Since MeV immunisation began, technological evolution and genetic sequencing have further discovered other protein factors in the immune system. These include cytokines and chemokines like type I interferon (IFN), type II IFN or type III IFN discovered between 1957 to 2003 alongside a host of Pattern Recognition Receptors (PRR) like Toll–like receptors (TLR) amongst others.

During a 10–year study following MeV as well as Mumps virus (MuV) neutralising antibodies after immunisation, (n=98), comparisons were made between 7-17 post immunisation after that although did not indicate a statistical difference between either but did indicate that 42% of individuals experienced more than 20% waning of MeV antibody titres with an established antibody correlate (120 mIU/mL) [63]. Furthermore waning of IgG antibodies occurred specifically for MuV rather than neutralising antibodies [63]

In 2019, researchers in Boston in a crucial study observed in serological analysis (n=77), during natural MeV infection, that the host antibody repertoire was reduced by up to 73% during MeV natural infection in children [64]. Concurrent observations were the MeV epitope repertoire presented to the immune system during infection can be suppressed in NHP *in vivo* (n=4). Therefore this apparent immunosuppression caused by MeV may change or affect the human host's immune response to other pathogens including Herpesvirus, Papillomavirus amongst many other bacterial infections (e.g., *Streptococci*) for up to 5 months after natural infection with much unknown[64]. Recently between 2017–and 2021, B3/D8 genotypes were examined and genotyped during a MeV outbreak in Italy as B3/D8 (n=864) to show that breakthrough infections could occur in immunised individuals an estimate of <2.6% that were non–responsive to immunisation [25].

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} cellular count reduction, there was an accompanying reduction in antibody secretion of two predominant types within serum and mucosal compartments (IgG/IgA); although increases in other B cells, transitional B cells, were observed being bone marrow resident B cells [65]. Measles virus therefore has been confirmed to selectively deplete and affect naïve B cell development with signaling pathways largely unknown but potentially affecting the immune response during pathology [65].

During the acute phase of MeV infection, circulating B cells as well as T cells are infected through MeV adhesion to at least one receptor (CD46). Receptors are present throughout the lymphoid tissues, germinal centres (GCs) and draining lymph nodes (dLNs). On the other hand, MeV infection is associated with a robust immune response to MMR immunisation whilst infection is indicative of B and/or T cell temporal lack of memory cell response remaining unclear. In 2012, CD46 polymorphisms were genotyped in children (n=137) and shown to significantly correlate with IgG MeV specific levels with 1 genotype (*CD46 rs7144*) seemingly affecting both B and $CD3^{+}$ T cells rs7144, [66]. In this study, MeV

antibody titers below 324 mIU/ml were considered seronegative of which 10.2% of subjects did not produce antibodies [66]. Although in 2020, Australian reports (n=297) during MeV infection (2008-2017), outline that sometimes primary and secondary MeV vaccine failure could potentially be observed with antibody responses still present, denoted as nonimmune ($IgM^{+/-}/IgG^{-}$), indeterminate (IgM^{+}/IgG^{+}) but also waning immunity (IgM^{-}/IgG^{+}) further elucidating potential useful indicators [67].

Adaptive Immune Responses during Measles Virus Infection

In 2012 reports emerged investigating to show that both innate (B cells) and T cells could be infected by MeV[56]. The effector host cell response to MeV infection relies on many types of T cells. For example, effector T memory (T_{EM}) cells, but also recall of other helper T cell and cytotoxic T cell (T_H/T_C) responses to provide longer–term adaptive immunity. Other T cells include and are defined phenotypically as naïve (T_N), and regulatory T cells (T_{REGS}), whilst others secrete chemical cytokines like IL–17 (T_H17 cells) amongst other T cell phenotypes.

T cells can be infected through MeV fusion proteins binding to the plasma membrane barrier surrounded by receptors as above. The phenotypes affected include memory T lymphocytes lacking expression of receptor proteins like CD molecule proteins ($CD45RA^{-}$) or expressing other CD proteins ($CD45R0^{+}$) [56]. These specific T cells traverse and diffuse through endothelial cell layers (ECs), 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 types of T cells were preferentially infected that were T_{EM} cells and central memory (T_{CM}) T cells, with the hypothesis that natural MeV infection induces immune cell temporal amnesia [29][56]. However, other types of cells that develop into B cells were observed as proliferating within LNs (follicular B cells) measured by Ki67 a cellular marker of proliferation. Suggestions were that apoptosis did not occur as measured by caspase–3 expression within T cells, but rather that MeV–infected cells were preferentially killed by T_C cells producing an array of effector enzymes like perforins and granzymes [29][56].

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 above that the attenuated MeV particle and resulting cell–derived processed epitopes can be presented by the immune cell phenotypes expressing CD46 and therefore be metabolised [64]. 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 [68].

More recent research of MeV infection (n=26) are indicative of other T cell subtypes affected. These are follicular T helper cells (T_{FH}), 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 [69]. Below is a depiction of some of the immunological cells and proteins pertaining to MeV infection (See Figure 4).

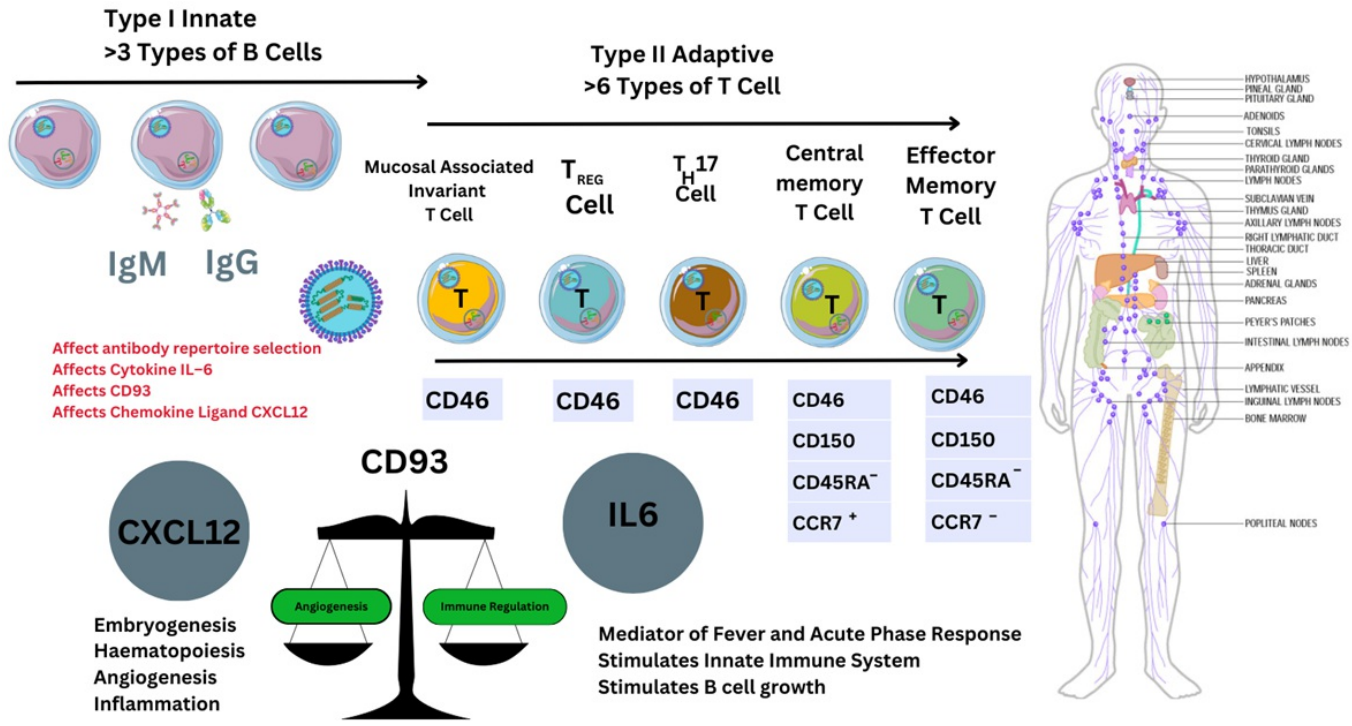

Figure 4. Characteristics of the Innate and Adaptive Immune Response to Measles Infection

Comparatively less is known about the role of Natural Killer (NK) cells during MeV infection or other immune cell phenotypes. However, since the 1954 isolation of MeV, many of the T cell phenotypes further are defined by the expression of chemokines (CXC/CCR) and respective ligands (CXCL) alongside CD membrane proteins by T cells. These are commonly denoted by the leukocyte common antigen (CD45), and CCR7 is frequently expressed by naïve T cells (T_N). The phenotypes observed to be infected in NHP with MeV infection were T central memory (T_{CM}) cells ($CD45RA^-CCR7^+$), or effector memory (T_{EM}) cells ($CD45RA^-CCR7^-$) expressing SLAMF1 (CD150) [56][70]. Similarly, MeV is known to infect naive B cells (IgD^+CD27^-), or memory B cells (IgD^-CD27^+), as well as other B cells ($CD20^+$) expressing an APC receptor, the type II major histocompatibility complex (MHC) receptor (HLA–DR) [56][70].

Chemokine Expression during Measles Virus Infection

During 2011, as chemokine research evolved, the role of CXCL12 was investigated, and considered to be affected that may potentially affect APCs. It was then postulated that *RUNX3,* a regulatory transcription factor could regulate and maintain CD4 and CD14 expression thereby affecting monocyte differentiation with individual angiogenic and immunosuppressive activity [71][72]. This chemokine, CXCL12, is known as a B cell developmental growth factor also called stromal–derived factor 1α (SDF–1α).

Further reports in 2016, using unbiased mRNA–sequencing technology, indicated that immunisation against MeV elicited the production through cellular messenger RNA of three key proteins that were CD93, IL6, as well as CXCL12 [73]. As mentioned above, CXCL12 protein synthesis was observed to be downregulated during MeV infection. 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 function discovered with a negative correlation to T_H1, NK cells, but also myeloid–derived suppressor cells (MDSC) in cancer as well as follicular T helper (T_{FH}) cells [74]. It was furthermore considered that blockade of CD93 could sensitise tumours to immune–checkpoint therapy [74]. Whereas, IL–6 is a well–characterised cytokine performing a role as a chemoattractant for neutrophils during pro–inflammatory immune responses; whilst CD93 is found expressed by cell lineages including myeloid cells, haematopoietic stem cells (HSPCs), Natural Killer (NK) cells and platelets concurrently with neuronal, microglial and endothelial cells (ECs) [75]. It was further clarified that IL–2 along with tumour necrosis factor (TNF–α) and a type II interferon (IFN–γ) are required for effective innate host responses during MeV infection. Previous articles indicate that increases in levels of soluble IL–2R (CD25) a marker of T_{REGS} only discovered in the 21st century occur with cyclical IL–17 changes produced by T_H17 cells and others. This is unsurprising and a cytokine tumour necrosis factor (TNF–α) is also expressed within epithelial cellular layers during infection, but also during premalignant oncological conditions, where epithelial layers differentiation is affected [76][77].

In 2017, the T cell response was further analysed indicative that $CD4^+$ T cells produce IFN–γ during the MeV infection rash period along with cytokines required for Mϕ maturation into either M1ϕ or M2ϕ phenotypes (IL–4, IL–10 and IL–13) [78]; whilst antibody production occurs in a T_H1 type response considered to be beneficial. However, other cytokines like IL–17 were synthesised and secreted up to 126 days after infection whilst the other 2 key types of T cells that include T_{REGS} and T_H17 cellular actions have not as yet been measured [78]. Both of the two cell types expressed RORγt (retinoic acid nuclear receptor); furthermore, both were shortly after clarified to be specific for the MeV H and N proteins. [79].

Development in 2020 indicated that a second chemokine, CXCL10, found in serum concentrations could be a correlate of severity during MeV infection [80]. These were interesting observations because the receptor for CXCL10 is CXCR3 expressed on many immune cells that include DCs in varying degrees that are required for antigen presentation. More recently it was observed that MeV infects cytokeratin–positive epithelial cells in bronchial and appendix epithelia with disruption of alveolar and bronchial epithelial cells and multinucleated cells expressing CD11c characteristic of the dendritic cell population (DC) or the macrophage (Mϕ) cells expressing CD68 [81]. Further details remain unknown.

In 2003, when type III IFN was discovered, it was indicated that the MeV C protein may suppress type I IFN (IFN–α or IFN–β) [82]. The resultant inhibition by MeV infection of the Janus kinase (JAK1) enzyme crucial to nuclear IFN signal transduction, thereby in effect may temporarily modulate the type I IFN response required, in effect altering type I IFN synthesis with research continuing [83]. More recently, since type III IFN discovery, in 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[84].

More recently since 2021, it is apparent that MeV can modulate mitochondrial DNA (mtDNA) throughout MeV infection in common with both +ssRNA and –ssRNA viruses whilst affecting the cyclic GMP–AMP synthase (cGAS) pathway that potentially stimulate each of type I/II/III IFN secretion pathways required for immune responses [85][86]. Therefore it could be apparent that MeV differential proteins could modulate the IFN systemic response essential to antiviral innate/adaptive

cellular reactions unknown so far.

As recently as 2021, other emerging reports further confirm that MeV infects recently characterised mucosal–associated invariant (MAIT) cells expressing $CD3^+$ with MHC class I–related gene protein (MR1), alongside invariant NK (iNKT) cells denoted by $CD3^+CD1d^+$ [87][88]. These were crucial because the MR1 protein can bind to other vitamin metabolites such as those produced during riboflavin synthesis (vitamin B2) during bacterial infection with others unknown [89][90][91][92]. Other T cell phenotypes are defined that include γδ T cells that could be a factor unknown so far amongst others like Vγ9Vδ2 T cells in the developmental immune response [93]

Limitations

Above some of the research will have included *in vivo / in vitro* research studies. Immunisation is subject to both regulatory and local authority jurisdiction for further guidance (See Supplementary Materials). Safety monitoring of immunisation occurs and is of consideration and discussed elsewhere, whilst similarly, vaccine efficacy remains difficult to quantify during MeV–caused disease which predominantly occurs in either infants or immunocompromised individuals [94][95].

Discussion

In recent years the European Centre for Disease Control and Prevention (ECDC) surveillance indicates that the incidence of Measles between 2014-2016 was (7.1-9.0 per million population). Following this within the EU (2017), there was an approximately four–fold increase in incidence (28.3 cases per million), in 2018 (34.4 cases per million), whilst in 2019, 25.4 cases per million population remained above those observed before (See Supplementary Materials). In 2022, World Health Organisation (WHO) reports indicate that 40,366 cases were reported in India, 23,983 in Nigeria, 552 in China, 63 in the UK, 7704 in Indonesia, and 14 in the USA subject to ongoing surveillance (see Supplementary Materials).

The rates of MeV disease are affected by a myriad of factors as well as immunisation evoking long–term innate and adaptive immune system responses. It is currently indicated that rare complications of measles diseases can be acute encephalitis and sclerosing panencephalitis occurring 7-10 years after initial MeV infection [1]. The most recent mortality data in 2018 indicative of overall MeV disease fatality globally indicates between 140,000 individuals affected predominantly under the age of 5 and also immunocompromised individuals [1]. This is affected by other factors including vaccine hesitancy, but also implementing immunisation programmes and schedules through cooperation globally [96][97] It is considered that immunisation coverage exceeding 90% or 95% could potentially lead to near eradication of MeV similar to other viruses like variola virus long since extinct [97].

Nevertheless, as above, immunological responses to the attenuated MeV since MMR immunisation inception could be longer than 10 years remaining unknown. This has been observed through a reduction in overall MeV disease case counts and disease burden since the progressive introduction of immunisation in various countries [98][99]. Given the high

seroconversion rates observed through MMR immunisation, it could be considered that vaccines targeting MeV may still lead to eradication in future, although unknown genetic factors can affect the immune response to the attenuated MeV [97]. Differential MeV measles antibody profiles were examined in China (n=2629) recently[100]. These were indicative of potential antibody threshold at around 14.3 years of age with antibody concentrations around 200 mIU/ml [100]. However, T–cell responses are complicated and can vary by age adding to the complexities[101]. The arbitrary scale of antibody responses is being compared globally with the complexity of variance in reagents used determined by the specificity and sensitivity of the monoclonal antibody [102]. It was thus indicated that the timing of immunisation could affect the comparatively efficacious nAb response during MeV immunisation programmes usually in infants [103].

Whilst CD150 was confirmed as a key MeV cellular entry receptor before 2018, it was noted that MeV seemingly infects T_N cells and B_{MEM} cells as well as both DCs, and M1ϕ/M2ϕ, but not the other key APCs that are monocytes*in vivo.* Research and laboratory research opinions vary on whether MeV infects monocytes, however, historically this was observed in 1975 research [104][105]. MeV may appear causal in the cytotoxic activity of lymphocytes entering B cell follicles between acute to severe MEV infection [69].

Seemingly, MeV immunosuppression has utility beyond what was originally known, with the role of T_{REGS} and NK cells remaining unknown. However, one project in 1990 examined NK cell responses which did appear unresponsive but could be rescued *in vitro* by the DC maturation/stimulation cytokine IL–12[106]. Cytolytic activity of *Paramyxoviridae* is known in similar viruses of this family like the Nipah virus [9]. Other factors largely unknown that MeV affects during disease were noted in France in 2017 when a trace element, selenium (n=94), was found to be reduced in the sera of individuals with acute MeV disease [107][108]. These were interesting findings because selenium is considered to be a required trace mineral essential to human health [108][109]. Whilst just prior in 2011, a systematic review examined synthetic Vitamin A supplementation in infants aged 6 months to 5 years as reducing overall mortality by up to 30% [110]. Vitamin A effects on the immune system newer phenotypes remain comparatively unknown as the STRA6 receptor was discovered in 2013 remaining central to vitamin A metabolism comparatively early in research [91]. Measles as a viral infection was examined during autoregressive models of immunisation within 10 vaccine–preventable diseases (1900-2015) to indicate that the effective reduction by cases in order of disease is diphtheria, mumps, chickenpox and then measles [111]. Other recent studies before and since the recent SARS–CoV–2 pandemic are indicative that CD150 has a role in DC maturation. Since other DC phenotypes were observed between 2006-2018 and specifically in 2017, further developments will be interesting to see [112][113]. Interestingly to our knowledge, the polymorphisms of CD46 were only observed in 2012, at least with attenuated MeV strains, where CD46 was highly expressed on monocytes but also a specific genotype (7144CC) may affect CD46 expression by T cells and resultant activation, but also the host response to MeV immunisation [66].

Conclusions

The longevity of humoral or adaptive correlates to MeV infection or vaccine correlates remains unknown currently; although longitudinal studies point towards natural infection and immunisation against MeV inducing high concentrations

of neutralising antibodies preventative of pathogenic diseases. Therefore the relevance of MeV as an infectious disease is that the production of neutralising antibodies or recalled memory B and T cell responses potentially have a duration of at least 10 years or more. But different infections or diseases can have individually different immunological responses. Measles immunisation seemingly induces host antibody types that predominantly completely block and/or reduce MeV cellular replication. The role of type III IFN in MeV infection remains unknown as other deficiencies can occur that affect both host viral and bacterial immune responses during development and throughout life [114]. Above the role that both the innate and adaptive immune cells is outlined in response to MeV infection underpinning how immunisation evokes a host response.

At this time 2 MeV accessory proteins (C/V) are known that could affect the type I IFN receptor complex signal transduction and activator of transcription (STAT1/2) proteins. Further details will be outlined in our next articles on the type I/II/ III IFN pathways during infectious diseases or immunodeficiency (See Supplementary Materials). Therefore innate immune responses to MeV infection may be independent of type I/III IFN synthesis with much remaining unknown with research ongoing.

Currently, 129 clinical trials investigating measles infection have been completed with 8 in progress (see Supplementary Materials). Beyond the outline above, comparatively much remains unknown on the replication mechanisms that the wild–type measles virus utilises within cells but is indicated to form inclusion bodies [30][115][116]. 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 antigenic variation, much remains unknown on a pathogen that has high transmission rates affecting predominantly infants under the age of 5. Future research should therefore consider the other T cell phenotypes and transcriptome studies.

Supplementary Materials: Manual for the Laboratory–based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome – TechNet–21; Measles – Annual Epidemiological Report for 2022 (europa.eu): Measles – number of reported cases (who.int); WER9030_373-380.PDF (who.int); Search Results | Beta ClinicalTrials.gov; History of measles vaccination (who.int); human rabies immunoglobulin: List of nationally authorised medicinal products – PSUSA/00001639/201704 (europa.eu); Antibody therapeutics approved or in regulatory review in the EU or US – The Antibody Society; https://www.who.int/health–topics/poliomyelitis/; Measles Elimination in the U.S. | CDC; Measles – number of reported cases (who.int); Measles (who.int); Rinderpest – WOAH – World Organisation for Animal Health; https://www.who.int/data/gho/data/indicators/indicator–details/GHO/measles–-umber-of-reported-cases; David Edmonston and the Measles Vaccine - VAXOPEDIA; Measles number of cases by region worldwide 1980-2021 | Statista; Measles Complications | CDC; Genetic Analysis of Measles Virus | CDC; IEDB.org: Free epitope database and prediction resource; Measles and Rubella Laboratory Network (who.int); National Center for Biotechnology Information (nih.gov); Encephalitis | National Institute of Neurological Disorders and Stroke (nih.gov) Vaccine Scheduler | ECDC (europa.eu); Measles: the green book, chapter 21 - GOV.UK (www.gov.uk)

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Author contributions

BB: Conceptualization, Methodology, Formal analysis, Writing—review & editing, Data curation, Writing—original draft, Visualization, Software, Supervision.

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