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

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Abstract

Measles is a virus, abbreviated to MeV, thought to have existed around 4000 years ago that has long been known to be causal in infant disease affecting mortality and remaining a public health issue. The causal virion is defined biologically within the Family *Paraxmyxoviridae*, Genus *Morbillivirus* and Species *MeaslesMorbillivirus.* Similar to other infections, MeV is an airborne infection with the virion particle composed of a negative (-ve) sense single–stranded (ss) ribonucleic acid (RNA) genome code, around 15-16kb in size, encoding for eight predominant proteins. The first isolation of MeV occurred in 1954 of MeV known as the “Edmonston strain” from David Edmonston, a student at Fay School in Boston. The lack of antigenic variation by the MeV particle 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. 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.* This occurs through barriers known as the glycocalyx and endothelial surface layer (GC-ESL) together with immunological cell phenotypes that can restrict viral replication through respiratory epithelial and endothelial cell layers affected by MeV. Other proteins like cytokines, chemokines as well as adhesion molecules and receptors direct immune cell systems. Therefore it was then observed that a preventative chemical could inactivate pathogenic infection. Here is a discussion of contextual MeV immunological characteristics during infection. Potential explanations to elucidate this further with regards 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 was utilised largely since 1971 predominantly utilising a weakened or “attenuated” MeV strain, but also a formalin-inactivated vaccine developed [1]. This attenuation can restrict viral replication in cells and tissues and generate an immune response. 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 which vary 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].

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. (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. 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), as recently both MeV and Nipah virus (NiV) are known to cause severe neurological diseases including blindness and brain damage through unknown cellular mechanisms in a minority of infections [1][3][7][8][9]

Immunisation against Measles virus (MeV) is considered to induce long–term immunity; however little is known about the underlying biological mechanisms so far of how this occurs during natural infection [1][10]. Two other MeV strains since the original Edmonston strain discovery, are utilised that are “Schwarz” and “Moraten” derived from the original “Edmonston” MeV strain [1]. The MeV virion particle is comparatively considered to be a potential viral vector that can be engineered to target other viral pathogens like Human Immunodeficiency virus (HIV), Dengue Fever virus (DENV) as well as Chikungunya virus (CHIK) 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 long known as the original attenuated vaccine-utilised strain of MeV can infect host cells expressing one receptor, the cluster of differentiation molecule (CD46), and induce an active immune response causal in long–term immunogenic host responses, with similarities to the Vaccina virus (VACV) utilised as well (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]. 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 efficacy of more than 90% to either the trivalent or quadrivalent options that were manufactured and designed to counter Varicella Zoster (VZV) virus viral antigen epitopes [1][19]. However, more recently it has been indicated that current measles 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 and training the innate and adaptive immune system response [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 –ssRNA strand (see Supplementary Materials) [20]. This encodes the nucleoprotein (N), followed by a conserved Haemagglutinin (H) protein and then a fusion (F) protein, matrix (M) protein followed by a trimer of a **phosphoprotein (P) and 2 non-structural proteins (**C/V) followed by a larger polymerase (L) enzyme towards the 5' end of the RNA genome. The L protein polymerase sequentially transcribes by binding to the MeV RNA at the 3' leader with polyadenylation occurring during synthesis with V protein produced through RNA editing and a P protein produced from the C protein. 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]. Whilst 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]

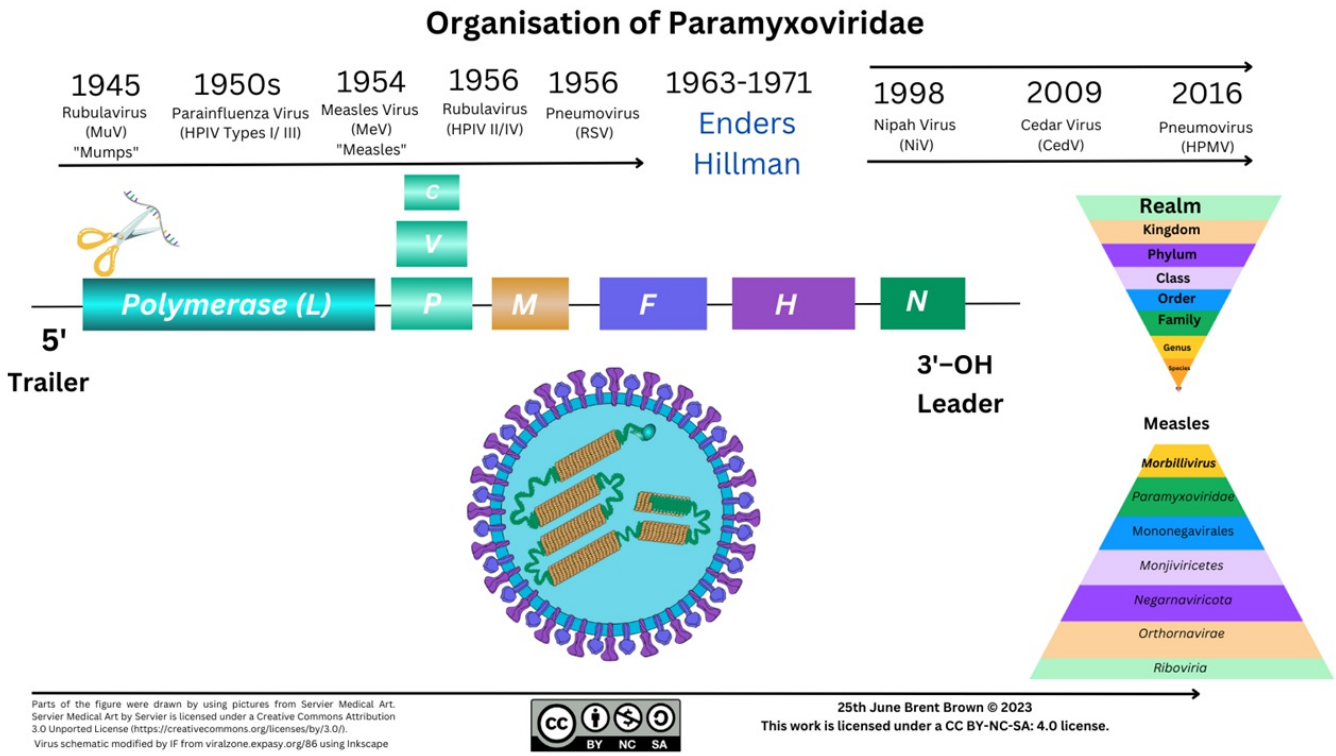

Figure 1. Organisation of Paramyxoviridae

History of Measles

Genetic characterisation of the MeV virus particle indicates ancestry around 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) conferring resistance to monoclonal antibodies then [33].

More recently in 2015, investigations during outbreaks in Canada occurred of specific MeV H1 and D8 strains [34] Previously 24 known genotypes had been sequenced. Indeed in 2018, the MeV genotypes in global circulation decreased to 4 in 2018. These were denoted by two MeV strains (B3/D8) together with two others (D4/H1) globally during 2020 [35]. Out of these, two (B3/D8) are known to be endemic across six of the WHO regions[36].

Development of Measles Research

Many viral protein point mutations can affect immunologically programmed responses to pathogens. During 2009 as monoclonal antibody 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) [37]. It is considered that this cellular receptor is expressed by many nucleated cells [37]. 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. 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][38]. 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]. Variability in immune response generated to the attenuation and wild-type MeV is discussed further predominantly by immune cell phenotypes below.

Measles Receptor-Mediated Infection

Measles cellular infection was further researched after immunisation with the attenuated virus to occur through one receptor (CD46, SLAMF1) [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 [39][40][41].

To this effect, research in Germany in 1993 by Dorig and Naniche showed that CD46 could be inhibited by two both types

of antibodies [37]. The two types of antibodies then were 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 [37]. 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 signaling 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 [37][42]. 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, 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) as well as on platelets and haematopoietic stem cells (HPSC). 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 [40]. Nectin–4 clarification came as recently as 2012, similar to other types of poliovirus receptors (PVR) documented prior, like CD155 [41]. 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 [43].

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. However, recently chemokines also can affect the checkpoint balancing immune cell signaling in an autocrine/paracrine fashion similar to other hormones [29]. Measles particle virions disturb this normal homeostatic cellular function in 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 of the brain (e.g., subacute sclerosing panencephalitis (SSPE)) [24]. This is a lesser observed phenomenon indicated at 6.5-11 cases per 100,000 but occurring some years after infant MeV infection but the blood-brain barrier was historically considered to be an immune privileged barrier [24].

Innate Immune Responses during Measles Infection

The phenomenon of vaccine failure has been known for 50 years since Cherry et al. described outbreaks between 1971-1973 [44][45]. The reasons for this remain unknown. Early indicators in 2001 appeared examining natural MeV infection, as

duration and kinetics of the immune response remain of interest. Kinetics of the immune response indicate 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* [46]. 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 while the cellular memory response develops alongside with switching between antibody types documented largely after this, with IgG4 appearing later after MeV infection [47]. Population serology studies in 2020 (n=1092) examined neutralising antibodies (nAbs) between 10-12 years after either infection or immunisation against MeV [48][49]. 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 [47].

Other research indicates 4 years after MeV infection that IgG2 and an unknown antibody subtype of IgG2 were relevant during convalescence [50]. During natural MeV infection, IgG1 and IgG3, remain the dominant earlier humoral antibodies produced [50]. These were interesting observations because, *in vivo,* in mice rather than humans, there are observed to be a further 3 subtypes of IgG2 [51][52][53]. 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 7.6-14.2 years 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) [54].

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 [55]. 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 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[55]. Recently between 2017-2021, 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 natural infection, it was similarly observed that B memory (B_{MEM}) cells were reduced that would usually develop and stimulate other cells to form antibody–secreting cells (ASCs). Together with B_{MEM} cellular count reduction there was accompanying reduction in antibody secretion of two predominant types within serum and mucosal compartments (IgG/IgA); interestingly increases in other B cells, transitional B cells, were observed being bone marrow resident B cells [56]. 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 [56].

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, [57]. In this study, MeV antibody titers below 324 mIU/ml were considered seronegative of which 10.2% of subjects did not produce antibodies [57]. Although recently in 2020, Australian reports (n=297) between 2008-2017 outline that primary and secondary MeV vaccine failure could potentially be observed with antibody responses still present, denoted as nonimmune ($IgM^{+/-}/IgG^-$), indeterminate (IgM^+/IgG^+) and waning immunity (IgM^-/IgG^+)[58].

Adaptive Innate Immune Responses during Natural Measles Infection

In 2012 reports emerged investigating to show that both innate (B cells) and T cells could be infected by MeV[46]. The effector host cell response to MeV infection relies on many types of T cells. For example, effector 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 that are infected by MeV include memory T lymphocytes lacking expression of receptor proteins like CD molecule proteins ($CD45RA^-$) or expressing other CD proteins ($CD45R0^+$) [46]. 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 also central memory (T_{CM}) T cells, with the hypothesis that natural MeV infection induces immune cell temporal amnesia [29][46]. 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][46].

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 [55]. Recent diagnostics commonly used up to 5 days after infection are real–time polymerase chain reaction (rtPCR); whilst serology assays have been reviewed elsewhere available for MeV indicative of sensitivity of 90.6% but also 100% specificity to date [59].

More recent outbreaks of natural MeV infection (n=26) are indicative that other T cell subtypes are 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 [60].

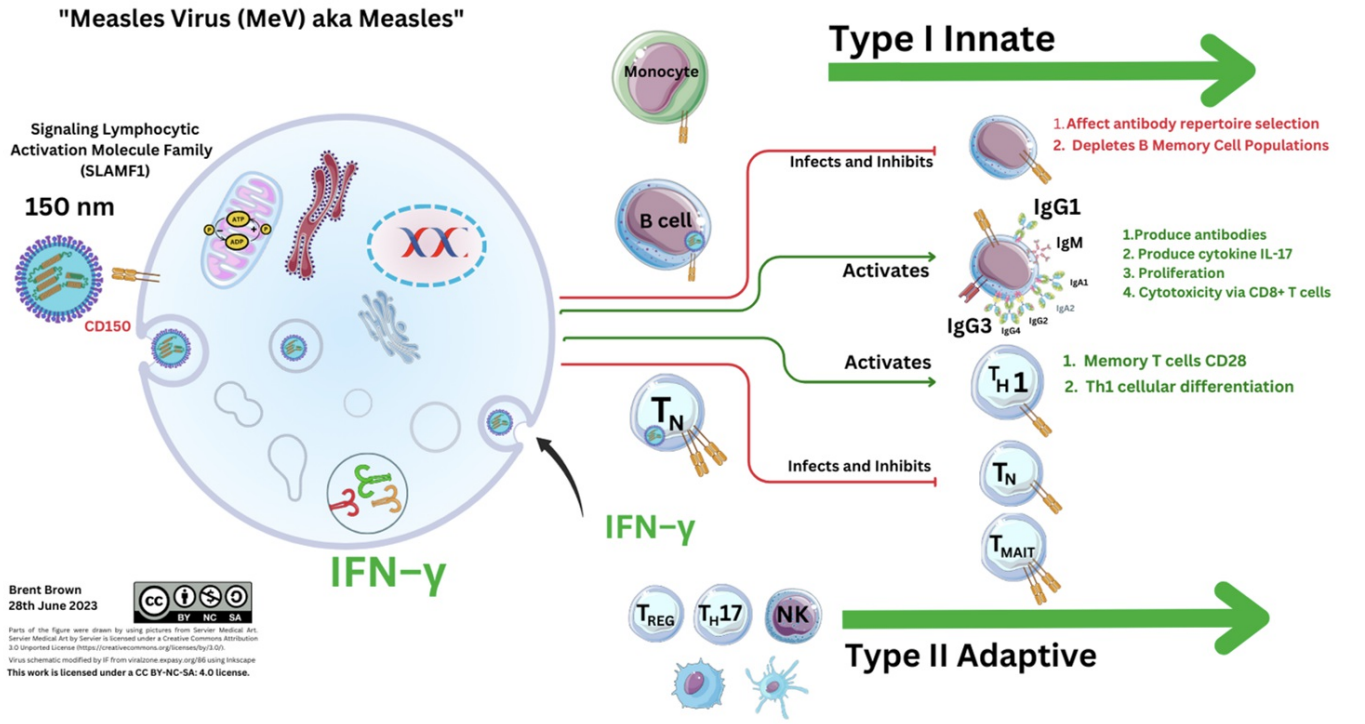

Figure 2. Measles Infection of Immune Cells

Comparatively less is known about the role of Natural Killer (NK) cells during MeV infection or other immune cell phenotypes in prior reviews. However, since the 1954 isolation of MeV, many of the T cell phenotypes further are defined by expression of chemokines (CXC/CCR) as well as respective ligands (CXCL) alongside CD cellular membrane proteins by T cells. These are commonly denoted by the leukocyte common antigen (CD45), but also the chemokine (CCR7) frequently expressed by naïve T cells (T_N). The phenotypes observed to be infected in NHP were T central memory (T_{CM}) cells ($CD45RA^-CCR7^+$), or effector memory (T_{EM}) cells ($CD45RA^-CCR7^-$) expressing increased levels of CD150. Similarly 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) [46][61].

Chemokine Expression during Natural Measles 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[62][63]. This chemokine, CXCL12, is known as a B cell developmental growth factor also called stromal–derived factor 1α (SDF–1α).

Further reports emerged in 2016 using unbiased mRNA–sequencing technology indicating that immunisation against MeV elicited the production through cellular messenger RNA of three key proteins that were CD93, IL6, as well as CXCL12 [64]. 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 negative correlation to T_H1, NK cells, but also myeloid–derived suppressor cells (MDSC) and follicular T helper (T_{FH}) cells in cancer [65]. It was furthermore considered that blockade of CD93 could sensitise tumours to immune–checkpoint therapy [65]. Whereas, IL–6 is a well–well-characterised cytokine performing a role as a chemoattractant for neutrophils during pro–pro-inflammatory immune responses; whilst CD93 is found expressed by a wide variety of cell lineages including myeloid, myeloid cells, haematopoietic stem cells (HSPCs), Natural Killer (NK) cells and platelets concurrently with neuronal, microglial and endothelial cells (ECs) [66]. 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 occurs with cyclical IL–17 changes produced by T_H17 cells and others. This is unsurprising and a cytokine tumour necrosis factor (TNF–α) was previously considered expressed within epithelial cellular layers during infection, but also during pre-malingant oncological conditions, where epithelial layers differentiation is affected [67][68].

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) [69]; 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 [69]. Interestingly both of the two cell types expressed RORγt (retinoic acid nuclear receptor) [70]. These were shortly after clarified to be specific for the MeV H and N proteins) [70].

Development in 2020 indicated that a second chemokine, CXCL10, found in serum concentrations could be a correlate of severity during MeV infection [71]. 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 multi–nucleated cells expressing CD11c characteristic of the dendritic cell population (DC) or the macrophage (Mϕ) cells expressing CD68 [72]. Further details remain unknown.

More recently since 2021, it is apparent that MeV can modulate mitochondrial DNA (miDNA) throughout the course of MeV infection in common with both +ssRNA and –ssRNA viruses whilst affecting the cyclic GMP–AMP synthase (cGAS) pathway that potentially stimulate each of the type I/II/III IFN secretion pathways required for immune responses [73][74]. Therefore it could be apparent that MeV differential proteins could in fact modulate the IFN systemic response essential to antiviral innate/adaptive cellular reactions unknown so far.

This report would there indicative the crucial importance of immunisation against MeV that seemingly could share an abundance of epitopes with many other pathogens. 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 $CD3^+CD1d^+$ [75][76]. These were crucial because MR1 protein can bind to vitamin metabolites such as those produced during riboflavin synthesis (vitamin B2) during bacterial infection with others unknown [77][78][79][80]. Other T cell phenotypes are defined that include γδ T cells that could be a factor unknown so far and others like Vγ9Vδ2 T cells may play a part in the developmental immune response [81]

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). Adverse effects may occur and are of consideration but also similarly vaccine efficacy remain difficult to quantify during MeV-caused disease with other viral and bacterial infections influencing a factor [82][83]

Discussion

It is currently indicated that complications of measles are acute encephalitis and sclerosing panencephalitis can occur 7-10 years after initial MeV infection or others with the most recent mortality data in 2018 indicative of around 140,000 fatalities per annum [1]. Overall immunological responses could be longer than 10 years observed through a reduction in overall measles case counts and disease burden since the introduction of immunisation [84][85]. Differential MeV measles antibody profiles were examined in China (n=2629) recently [86]. These were indicative of potential antibody threshold at around 14.3 years of age with antibody concentrations around 200 mIU/ml [86]. However, T cell responses are known to be variable by age adding to the complexities [87]. 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 [88]. The resultant inhibition by MeV infection of the Janus kinase (JAK1) enzyme crucial to nuclear IFN signal transduction thereby in effect may modulate the type I IFN response required, in effect freezing the type I IFN pathway and IFN synthesis with research continuing [89].

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) [90]. 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[91]. It was thus indicated that the timing of immunisation could affect the comparatively efficacious nAb response during MeV immunisation programmes usually in infants under 4 years old [92]. 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 opinion varies on whether MeV infects monocytes, however historically this was observed in 1975 research [93][94]. MeV may appear causal in cytotoxic activity of lymphocytes entering B cell follicles between acute to severe MEV infection [60]. 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 [95]. 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 [96][97]. These were interesting findings because selenium is considered to be a required trace mineral essential to human health [97][98]. 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% [99]. Vitamin A effects on the immune system newer phenotypes remains comparatively unknown as the STRA6 receptor was discovered in 2013 remaining central to vitamin A metabolism comparatively early in research [79]. Measles as a viral infection was examined furing autoregressive models of immunisation within 10 vaccine–preventable diseases (1900-2015) to indicate that the effective reduction by case in order of disease is diphtheria, mumps, chickenpox and then measles [100]. 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 [101][102]. Interestingly to our knowledge, the polymorphisms observed in 2012 seem to indicate that, at least with attenuated MeV strains, that CD46 was highly expressed on monocytes but also a specific genotype (7144CC) specifically may affect CD46 expression on T cells and resultant activation [57].

Conclusions

The longevity of either humoral or adaptive correlates to MeV infection or vaccine correlates remains unknown currently; although longitudinal studies point towards a natural infection and immunisation against MeV inducing high concentrations of neutralising antibodies (nAb) that can be 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, but different infections or diseases can have individually different immunological responses. Measles immunisation seemingly induces antibody types that completely block the method of viral entry to the cell and replication. The role of type I/III IFN in MeV infection remains unknown and deficiencies can occur that affect both

host viral and bacterial immune responses during development.

At this time 2 MeV accessory proteins (C/V) were examined that could interfere with the type I IFN receptor (IFNAR1) complex by binding to signal transducer and activator of transcription (STAT1) protein. Further details will be outlined in our next articles on the type I/II and type III IFN pathways during infectious diseases or immunodeficiency (See Supplementary Materials). Therefore during natural MeV infection innate immune responses may be independent of type I/III IFN synthesis with much remaining unknown.

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 mechanisms that MeV utilises within cells but is indicated to form inclusion bodies (IBs) within cells [30][103][104]. Given this, clarity will further be required as to how other T cells are affected by MeV infection. Despite the comparative success of immunisation to date and lack of antigenic variation, much remains unknown on a pathogen that has high transmission rates and affects 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–-number-of-reported-cases; David Edmonston and the Measles Vaccine - VAXOPEDIA; Measles number of cases by region worldwide 1980-2021 | Statista; Measles Complications | CDC

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References

1. [a, b, c, d, e, f] *Griffin, D.E. Measles Vaccine. Viral Immunol 2018, 31, 86–95, doi:10.1089/vim.2017.0143.*
2. [a, b] *Conis, E. Measles and the Modern History of Vaccination. Public Health Reports 2019, 134, 118–125, doi:10.1177/0033354919826558.*
3. [a, b, c] *Tulchinsky, T.H. Maurice Hilleman: Creator of Vaccines That Changed the World. In Case Studies in Public Health; Elsevier, 2018; pp. 443–470.*
4. [^] *Stuart-Harris, C. The Contribution of Virology to Contemporary Medicine. J Epidemiol Community Health (1978) 1975, 29, 1–17, doi:10.1136/jech.29.1.1.*
5. [^] *Sbarra, A.N.; Jit, M.; Mosser, J.F.; Ferrari, M.; Cutts, F.; Papania, M.; Kretsinger, K.; McCarthy, K.A.; Thakkar, N.; Gaythorpe, K.A.M.; et al. Population-Level Risk Factors Related to Measles Case Fatality: A Conceptual Framework Based on Expert Consultation and Literature Review. Vaccines (Basel) 2023, 11, 1389, doi:10.3390/vaccines11081389.*
6. [^] *Bellini, W.J.; McFarlin, D.E.; Silver, G.D.; Mingioli, E.S.; McFarland, H.F. Immune Reactivity of the Purified Hemagglutinin of Measles Virus. Infect Immun 1981, 32, 1051–1057, doi:10.1128/iai.32.3.1051-1057.1981.*
7. [^] *Fisher, D.L.; Defres, S.; Solomon, T. Measles-Induced Encephalitis. QJM 2015, 108, 177–182, doi:10.1093/qjmed/hcu113.*
8. [^] *Fisher, D.L.; Defres, S.; Solomon, T. Measles-Induced Encephalitis. QJM 2015, 108, 177–182, doi:10.1093/qjmed/hcu113.*
9. [a, b, c] *Brown, B.; Gravier, T.; Fricke, I.; Al-Sheboul, S.A.; Carp, T.-N.; Leow, C.Y.; Imarogbe, C.; Arabpour, J. Immunopathogenesis of Nipah Virus Infection and Associated Immune Responses. Im-muno 2023, 3, 160–181, doi:10.3390/immuno3020011.*
10. [^] *Lin, L.-T.; Richardson, C. The Host Cell Receptors for Measles Virus and Their Interaction with the Viral Hemagglutinin (H) Protein. Viruses 2016, 8, 250, doi:10.3390/v8090250.*
11. [^] *Cherian, N.; Bettis, A.; Deol, A.; Kumar, A.; Di Fabio, J.L.; Chaudhari, A.; Yimer, S.; Fahim, R.; En-dy, T. Strategic Considerations on Developing a CHIKV Vaccine and Ensuring Equitable Access for Countries in Need. NPJ Vaccines 2023, 8, 123, doi:10.1038/s41541-023-00722-x.*
12. [^] *Mühlebach, M.D.; Hutzler, S. Development of Recombinant Measles Virus-Based Vaccines. In; 2017; pp. 151–168.*
13. [^] *Ammour, Y.; Susova, O.; Krasnov, G.; Nikolaeva, E.; Varachev, V.; Schetinina, Y.; Gavrilova, M.; Mitrofanov, A.; Poletaeva, A.; Bekyashev, A.; et al. Transcriptome Analysis of Human Glioblastoma Cells Susceptible to Infection with the Leningrad-16 Vaccine Strain of Measles Virus. Viruses 2022, 14, 2433, doi:10.3390/v14112433.*
14. [^] *Engeland, C.E.; Ungerechts, G. Measles Virus as an Oncolytic Immunotherapy. Cancers (Basel) 2021, 13, 544, doi:10.3390/cancers13030544.*
15. [^] *Pidelaserra-Martí, G.; Engeland, C.E. Mechanisms of Measles Virus Oncolytic Immunotherapy. Cy-tokine Growth Factor Rev 2020, 56, 28–38, doi:10.1016/j.cytogfr.2020.07.009.*

16. [a, b]*Frantz, P.N.; Teeravechyan, S.; Tangy, F. Measles-Derived Vaccines to Prevent Emerging Viral Dis-eases. Microbes Infect 2018, 20, 493–500, doi:10.1016/j.micinf.2018.01.005.*
17. [^]*Guerra, F.M.; Bolotin, S.; Lim, G.; Heffernan, J.; Deeks, S.L.; Li, Y.; Crowcroft, N.S. The Basic Re-production Number (R 0) of Measles: A Systematic Review. Lancet Infect Dis 2017, 17, e420–e428, doi:10.1016/S1473-3099(17)30307-9.*
18. [^]*Sukumaran, L.; McNeil, M.M.; Moro, P.L.; Lewis, P.W.; Winiecki, S.K.; Shimabukuro, T.T. Adverse Events Following Measles, Mumps, and Rubella Vaccine in Adults Reported to the Vaccine Adverse Event Reporting System (VAERS), 2003-2013. Clinical Infectious Diseases 2015, doi:10.1093/cid/civ061.*
19. [^]*Di Pietrantonj, C.; Rivetti, A.; Marchione, P.; Debalini, M.G.; Demicheli, V. Vaccines for Measles, Mumps, Rubella, and Varicella in Children. Cochrane Database of Systematic Reviews 2021, 2021, doi:10.1002/14651858.CD004407.pub5.*
20. [a, b]*Bankamp, B.; Takeda, M.; Zhang, Y.; Xu, W.; Rota, P.A. Genetic Characterization of Measles Vac-cine Strains. J Infect Dis 2011, 204, S533–S548, doi:10.1093/infdis/jir097.*
21. [a, b]*Norris, M.J.; Husby, M.L.; Kiosses, W.B.; Yin, J.; Saxena, R.; Rennick, L.J.; Heiner, A.; Harkins, S.S.; Pokhrel, R.; Schendel, S.L.; et al. Measles and Nipah Virus Assembly: Specific Lipid Binding Drives Matrix Polymerization; 2022; Vol. 8;.*
22. [a, b]*Fulton, B.O.; Sachs, D.; Beaty, S.M.; Won, S.T.; Lee, B.; Palese, P.; Heaton, N.S. Mutational Analy-sis of Measles Virus Suggests Constraints on Antigenic Variation of the Glycoproteins. Cell Rep 2015, 11, 1331–1338, doi:10.1016/j.celrep.2015.04.054.*
23. [a, b]*Bloyet, L.-M.; Schramm, A.; Lazert, C.; Raynal, B.; Hologne, M.; Walker, O.; Longhi, S.; Gerlier, D. Regulation of Measles Virus Gene Expression by P Protein Coiled-Coil Properties; 2019; Vol. 5;.*
24. [a, b, c]*Mathieu, C.; Bovier, F.T.; Ferren, M.; Lieberman, N.A.P.; Predella, C.; Lalande, A.; Peddu, V.; Lin, M.J.; Addetia, A.; Patel, A.; et al. Molecular Features of the Measles Virus Viral Fusion Complex That Favor Infection and Spread in the Brain. mBio 2021, 12, doi:10.1128/mBio.00799-21.*
25. [a, b]*Bianchi, S.; Gori, M.; Fappani, C.; Ciceri, G.; Canuti, M.; Colzani, D.; Dura, M.; Terraneo, M.; Lamberti, A.; Baggieri, M.; et al. Characterization of Vaccine Breakthrough Cases during Measles Outbreaks in Milan and Surrounding Areas, Italy, 2017–2021. Viruses 2022, 14, doi:10.3390/v14051068.*
26. [^]*Brown, B. Immunopathogenesis of Orthopoxviridae: Insights into Immunology from Smallpox to Monkeypox (Mpox). 2023, doi:10.20944/preprints202307.0673.v1.*
27. [^]*Baxter, D. Active and Passive Immunity, Vaccine Types, Excipients and Licensing. Occup Med (Chic Ill) 2007, 57, 552–556, doi:10.1093/occmed/kqm110.*
28. [^]*Gerber, F.; Tetchi, M.; Kallo, V.; Léchenne, M.; Hattendorf, J.; Bonfoh, B.; Zinsstag, J. RABIES IMMUNOGLOBULIN: Brief History and Recent Experiences in Côte d'Ivoire. Acta Trop 2020, 211, 105629, doi:10.1016/j.actatropica.2020.105629.*
29. [a, b, c, d, e, f]*Brown, B.; Ojha, V.; Fricke, I.; Al-Sheboul, S.A.; Imarogbe, C.; Gravier, T.; Green, M.; Peterson, L.; Koutsaroff, I.P.; Demir, A.; et al. Innate and Adaptive Immunity during SARS-CoV-2 Infection: Bi-omolecular Cellular Markers and Mechanisms. Vaccines (Basel) 2023, 11, 408, doi:10.3390/vaccines11020408.*
30. [a, b]*Guseva, S.; Milles, S.; Jensen, M.R.; Schoehn, G.; Ruigrok, R.W.; Blackledge, M. Structure, Dynam-ics and Phase*

Separation of Measles Virus RNA Replication Machinery. Curr Opin Virol 2020, 41, 59–67.

31. ^*Zhou, Y.; Su, J.M.; Samuel, C.E.; Ma, D. Measles Virus Forms Inclusion Bodies with Properties of Liquid Organelles. J Virol 2019, 93, doi:10.1128/JVI.00948-19.*
32. ^*Kimura, H.; Saitoh, M.; Kobayashi, M.; Ishii, H.; Saraya, T.; Kurai, D.; Tsukagoshi, H.; Shirabe, K.; Nishina, A.; Kozawa, K.; et al. Molecular Evolution of Haemagglutinin (H) Gene in Measles Virus. Sci Rep 2015, 5, 11648, doi:10.1038/srep11648.*
33. ^*Schrag, S.J.; Rota, P.A.; Bellini, W.J. Spontaneous Mutation Rate of Measles Virus: Direct Estima-tion Based on Mutations Conferring Monoclonal Antibody Resistance. J Virol 1999, 73, 51–54, doi:10.1128/JVI.73.1.51-54.1999.*
34. ^*Gardy, J.L.; Naus, M.; Amlani, A.; Chung, W.; Kim, H.; Tan, M.; Severini, A.; Krajden, M.; Pud-dicombe, D.; Sahni, V.; et al. Whole-Genome Sequencing of Measles Virus Genotypes H1 and D8 During Outbreaks of Infection Following the 2010 Olympic Winter Games Reveals Viral Transmis-sion Routes. Journal of Infectious Diseases 2015, 212, 1574–1578, doi:10.1093/infdis/jiv271.*
35. ^*Brown, K.E.; Rota, P.A.; Goodson, J.L.; Williams, D.; Abernathy, E.; Takeda, M.; Mulders, M.N. Genetic Characterization of Measles and Rubella Viruses Detected Through Global Measles and Ru-bella Elimination Surveillance, 2016–2018. MMWR Morb Mortal Wkly Rep 2019, 68, 587–591, doi:10.15585/mmwr.mm6826a3.*
36. ^*Bianchi, S.; Canuti, M.; Ciceri, G.; Gori, M.; Colzani, D.; Dura, M.; Pennati, B.M.; Baggieri, M.; Magurano, F.; Tanzi, E.; et al. Molecular Epidemiology of B3 and D8 Measles Viruses through He-magglutinin Phylogenetic History. Int J Mol Sci 2020, 21, 4435, doi:10.3390/ijms21124435.*
37. a, b, c, d, e*Kemper, C.; Atkinson, J.P. Measles Virus and CD46. In Measles; Springer Berlin Heidelberg: Berlin, Heidelberg; pp. 31–57.*
38. ^*Brown, B. Dr Jekyll and Mr Hyde: From Two Branches of Immune Response to Three Types of In-terferon Response. 2023, doi:10.32388/PBXUF5.*
39. ^*Laksono, B.; de Vries, R.; McQuaid, S.; Duprex, W.; de Swart, R. Measles Virus Host Invasion and Pathogenesis. Viruses 2016, 8, 210, doi:10.3390/v8080210.*
40. a, b*Chatterjee, S.; Sinha, S.; Kundu, C.N. Nectin Cell Adhesion Molecule-4 (NECTIN-4): A Potential Target for Cancer Therapy. Eur J Pharmacol 2021, 911, 174516, doi:10.1016/j.ejphar.2021.174516.*
41. a, b*Noyce, R.S.; Richardson, C.D. Nectin 4 Is the Epithelial Cell Receptor for Measles Virus. Trends Mi-crobiol 2012, 20, 429–439, doi:10.1016/j.tim.2012.05.006.*
42. ^*Liszewski, M.K.; Atkinson, J.P. Membrane Cofactor Protein (MCP; CD46): Deficiency States and Pathogen Connections. Curr Opin Immunol 2021, 72, 126–134, doi:10.1016/j.coi.2021.04.005.*
43. ^*Bowers, J.R.; Readler, J.M.; Sharma, P.; Excoffon, K.J.D.A. Poliovirus Receptor: More than a Simple Viral Receptor. Virus Res 2017, 242, 1–6, doi:10.1016/j.virusres.2017.09.001.*
44. ^*Cherry, J.D.; Feigin, R.D.; Lobes, L.A.; Hinthorn, D.R.; Shackelford, P.G.; Shirley, R.H.; Lins, R.D.; Choi, S.C. Urban Measles in the Vaccine Era: A Clinical, Epidemiologic, and Serologic Study. J Pe-diatr 1972, 81, 217–230, doi:10.1016/S0022-3476(72)80287-7.*
45. ^*Fappani, C.; Gori, M.; Canuti, M.; Terraneo, M.; Colzani, D.; Tanzi, E.; Amendola, A.; Bianchi, S. Breakthrough Infections: A Challenge towards Measles Elimination? Microorganisms 2022, 10, 1567,*

doi:10.3390/microorganisms10081567.

46. [a, b, c, d, e, f] *de Vries, R.D.; McQuaid, S.; van Amerongen, G.; Yüksel, S.; Verburgh, R.J.; Osterhaus, A.D.M.E.; Duprex, W.P.; de Swart, R.L. Measles Immune Suppression: Lessons from the Macaque Model. PLoS Pathog 2012, 8, e1002885, doi:10.1371/journal.ppat.1002885.*
47. [a, b] *Isa, M.B.; Martínez, L.; Giordano, M.; Zapata, M.; Passeggi, C.; De Wolff, M.C.; Nates, S. Measles Virus-Specific Immunoglobulin G Isotype Immune Response in Early and Late Infections. J Clin Mi-crobiol 2001, 39, 170–174, doi:10.1128/JCM.39.1.170-174.2001.*
48. [^] *Anichini, G.; Gandolfo, C.; Fabrizi, S.; Miceli, G.B.; Terrosi, C.; Gori Savellini, G.; Prathyumnan, S.; Orsi, D.; Battista, G.; Cusi, M.G. Seroprevalence to Measles Virus after Vaccination or Natural Infec-tion in an Adult Population, in Italy. Vaccines (Basel) 2020, 8, 66, doi:10.3390/vaccines8010066.*
49. [^] *Carryn, S.; Feyssaguet, M.; Povey, M.; Di Paolo, E. Long-Term Immunogenicity of Measles, Mumps and Rubella-Containing Vaccines in Healthy Young Children: A 10-Year Follow-Up. Vaccine 2019, 37, 5323–5331, doi:10.1016/j.vaccine.2019.07.049.*
50. [a, b] *Toptygina, A.P.; Pukhalsky, A.L.; Alioshkin, V.A. Immunoglobulin G Subclass Profile of Antimea-sles Response in Vaccinated Children and in Adults with Measles History. Clinical and Vaccine Im-munology 2005, 12, 845–847, doi:10.1128/CDLI.12.7.845-847.2005.*
51. [^] *Wang, F.; Tsai, J.C.; Davis, J.H.; Chau, B.; Dong, J.; West, S.M.; Hogan, J.M.; Wheeler, M.L.; Bee, C.; Morishige, W.; et al. Design and Characterization of Mouse IgG1 and IgG2a Bispecific Antibod-ies for Use in Syngeneic Models. MAbs 2020, 12, doi:10.1080/19420862.2019.1685350.*
52. [^] *Kao, D.; Danzer, H.; Collin, M.; Groß, A.; Eichler, J.; Stambuk, J.; Lauc, G.; Lux, A.; Nimmerjahn, F. A Monosaccharide Residue Is Sufficient to Maintain Mouse and Human IgG Subclass Activity and Directs IgG Effector Functions to Cellular Fc Receptors. Cell Rep 2015, 13, 2376–2385, doi:10.1016/j.celrep.2015.11.027.*
53. [^] *Vidarsson, G.; Dekkers, G.; Rispens, T. IgG Subclasses and Allotypes: From Structure to Effector Functions. Front Immunol 2014, 5, doi:10.3389/fimmu.2014.00520.*
54. [^] *Kennedy, R.B.; Ovsyannikova, I.G.; Thomas, A.; Larrabee, B.R.; Rubin, S.; Poland, G.A. Differential Durability of Immune Responses to Measles and Mumps Following MMR Vaccination. Vaccine 2019, 37, 1775–1784, doi:10.1016/j.vaccine.2019.02.030.*
55. [a, b, c] *Mina, M.J.; Kula, T.; Leng, Y.; Li, M.; de Vries, R.D.; Knip, M.; Siljander, H.; Rewers, M.; Choy, D.F.; Wilson, M.S.; et al. Measles Virus Infection Diminishes Preexisting Antibodies That Offer Pro-tection from Other Pathogens. Science (1979) 2019, 366, 599–606, doi:10.1126/science.aay6485.*
56. [a, b] *Petrova, V.N.; Sawatsky, B.; Han, A.X.; Laksono, B.M.; Walz, L.; Parker, E.; Pieper, K.; Anderson, C.A.; de Vries, R.D.; Lanzavecchia, A.; et al. Incomplete Genetic Reconstitution of B Cell Pools Con-tributes to Prolonged Immunosuppression after Measles. Sci Immunol 2019, 4, doi:10.1126/sciimmunol.aay6125.*
57. [a, b, c] *Clifford, H.D.; Hayden, C.M.; Khoo, S.-K.; Zhang, G.; Le Souëf, P.N.; Richmond, P. CD46 Measles Virus Receptor Polymorphisms Influence Receptor Protein Expression and Primary Measles Vaccine Responses in Naive Australian Children. Clinical and Vaccine Immunology 2012, 19, 704–710, doi:10.1128/CVI.05652-11.*
58. [^] *Gibney, K.B.; Attwood, L.O.; Nicholson, S.; Tran, T.; Druce, J.; Healy, J.; Strachan, J.; Franklin, L.; Hall, R.; Cross,*

G.B. Emergence of Attenuated Measles Illness Among IgG-Positive/IgM-Negative Measles Cases: Victoria, Australia, 2008–2017. Clinical Infectious Diseases 2020, 70, 1060–1067, doi:10.1093/cid/ciz363.

59. ^*Lutz, C.S.; Hasan, A.Z.; Bolotin, S.; Crowcroft, N.S.; Cutts, F.T.; Joh, E.; Loisate, S.; Moss, W.J.; Osman, S.; Hayford, K. Comparison of Measles IgG Enzyme Immunoassays (EIA) versus Plaque Re-duction Neutralization Test (PRNT) for Measuring measles serostatus: A Systematic Review of Head-to-Head Analyses of Measles IgG EIA and PRNT. BMC Infect Dis 2023, 23, 367, doi:10.1186/s12879-023-08199-8.*
60. a, b*Laksono, B.M.; de Vries, R.D.; Verburgh, R.J.; Visser, E.G.; de Jong, A.; Fraaij, P.L.A.; Ruijs, W.L.M.; Nieuwenhuijse, D.F.; van den Ham, H.-J.; Koopmans, M.P.G.; et al. Studies into the Mecha-nism of Measles-Associated Immune Suppression during a Measles Outbreak in the Netherlands. Nat Commun 2018, 9, 4944, doi:10.1038/s41467-018-07515-0.*
61. ^*de Vries, R.; Duprex, W.; de Swart, R. Morbillivirus Infections: An Introduction. Viruses 2015, 7, 699–706, doi:10.3390/v7020699.*
62. ^*Sánchez-Martín, L.; Estecha, A.; Samaniego, R.; Sánchez-Ramón, S.; Vega, M.Á.; Sánchez-Mateos, P. The Chemokine CXCL12 Regulates Monocyte-Macrophage Differentiation and RUNX3 Expres-sion. Blood 2011, 117, 88–97, doi:10.1182/blood-2009-12-258186.*
63. ^*Cambier, S.; Gouwy, M.; Proost, P. The Chemokines CXCL8 and CXCL12: Molecular and Function-al Properties, Role in Disease and Efforts towards Pharmacological Intervention. Cell Mol Immunol 2023, 20, 217–251, doi:10.1038/s41423-023-00974-6.*
64. ^*Haralambieva, I.H.; Zimmermann, M.T.; Ovsyannikova, I.G.; Grill, D.E.; Oberg, A.L.; Kennedy, R.B.; Poland, G.A. Whole Transcriptome Profiling Identifies CD93 and Other Plasma Cell Survival Factor Genes Associated with Measles-Specific Antibody Response after Vaccination. PLoS One 2016, 11, e0160970, doi:10.1371/journal.pone.0160970.*
65. a, b*Zhang, Z.; Zheng, M.; Ding, Q.; Liu, M. CD93 Correlates With Immune Infiltration and Impacts Pa-tient Immunotherapy Efficacy: A Pan-Cancer Analysis. Front Cell Dev Biol 2022, 10, doi:10.3389/fcell.2022.817965.*
66. ^*Nativel, B.; Ramin-Mangata, S.; Mevizou, R.; Figuester, A.; Andries, J.; Iwema, T.; Ikewaki, N.; Gasque, P.; Viranaïcken, W. CD93 Is a Cell Surface Lectin Receptor Involved in the Control of the Inflammatory Response Stimulated by Exogenous DNA. Immunology 2019, 158, 85–93, doi:10.1111/imm.13100.*
67. ^*You, K.; Gu, H.; Yuan, Z.; Xu, X. Tumor Necrosis Factor Alpha Signaling and Organogenesis. Front Cell Dev Biol 2021, 9, doi:10.3389/fcell.2021.727075.*
68. ^*MOTA, F.; RAYMENT, N.; CHONG, S.; SINGER, A.; CHAIN, B. The Antigen-Presenting Envi-ronment in Normal and Human Papillomavirus (HPV)-Related Premalignant Cervical Epithelium. Clin Exp Immunol 2001, 116, 33–40, doi:10.1046/j.1365-2249.1999.00826.x.*
69. a, b*Nelson, A.N.; Putnam, N.; Hauer, D.; Baxter, V.K.; Adams, R.J.; Griffin, D.E. Evolution of T Cell Responses during Measles Virus Infection and RNA Clearance. Sci Rep 2017, 7, 11474, doi:10.1038/s41598-017-10965-z.*
70. a, b*Eberl, G. RORγt, a Multitask Nuclear Receptor at Mucosal Surfaces. Mucosal Immunol 2017, 10, 27–34, doi:10.1038/mi.2016.86.*
71. ^*Semmler, G.; Griebler, H.; Aberle, S.W.; Stiasny, K.; Richter, L.; Holzmann, H.; Weseslindtner, L. Elevated CXCL10 Serum Levels in Measles Virus Primary Infection and Reinfection Correlate With the Serological Stage and*

Hospitalization Status. J Infect Dis 2020, 222, 2030–2034, doi:10.1093/infdis/jiaa326.

72. ^*Allen, I. V.; McQuaid, S.; Penalva, R.; Ludlow, M.; Duprex, W.P.; Rima, B.K. Macrophages and Dendritic Cells Are the Predominant Cells Infected in Measles in Humans. mSphere 2018, 3, doi:10.1128/mSphere.00570-17.*
73. ^*Sato, H.; Hoshi, M.; Ikeda, F.; Fujiyuki, T.; Yoneda, M.; Kai, C. Downregulation of Mitochondrial Biogenesis by Virus Infection Triggers Antiviral Responses by Cyclic GMP-AMP Synthase. PLoS Pathog 2021, 17, e1009841, doi:10.1371/journal.ppat.1009841.*
74. ^*Brown, B. Innate and Adaptive Immune Response during Ebola and Filoviridae Infection: A Cellular Analysis to 2023., doi:10.13140/RG.2.2.24216.57603.*
75. ^*Rudak, P.T.; Yao, T.; Richardson, C.D.; Haeryfar, S.M.M. Measles Virus Infects and Programs MAIT Cells for Apoptosis. J Infect Dis 2021, 223, 667–672, doi:10.1093/infdis/jiaa407.*
76. ^*Flores-Villanueva, P.; Sobhani, N.; Wang, X.; Li, Y. MR1-Restricted T Cells in Cancer Immunother-apy. Cancers (Basel) 2020, 12, 2145, doi:10.3390/cancers12082145.*
77. ^*Chancellor, A.; Vacchini, A.; De Libero, G. MR1, an Immunological Periscope of Cellular Metabo-lism. Int Immunol 2022, 34, 141–147, doi:10.1093/intimm/dxab101.*
78. ^*Rodan Sarohan, A. STRA6: The Key to Inflammatory Pathways in COVID-19. Fortune Journal of Health Sciences 2023, 06, doi:10.26502/fjhs.098.*
79. a, b*Dhokia, V.; Macip, S. A Master of All Trades - Linking Retinoids to Different Signalling Pathways through the Multi-Purpose Receptor STRA6. Cell Death Discov 2021, 7, 358, doi:10.1038/s41420-021-00754-z.*
80. ^*Blaner, W.S. STRA6, a Cell-Surface Receptor for Retinol-Binding Protein: The Plot Thickens. Cell Metab 2007, 5, 164–166, doi:10.1016/j.cmet.2007.02.006.*
81. ^*Perriman, L.; Tavakolinia, N.; Jalali, S.; Li, S.; Hickey, P.F.; Amann-Zalcenstein, D.; Ho, W.W.H.; Baldwin, T.M.; Piers, A.T.; Konstantinov, I.E.; et al. A Three-Stage Developmental Pathway for Hu-man Vγ9Vδ2 T Cells within the Postnatal Thymus. Sci Immunol 2023, 8, doi:10.1126/sciimmunol.abo4365.*
82. ^*Bellavite, P.; Donzelli, A. Adverse Events Following Measles-Mumps-Rubella-Varicella Vaccine: An Independent Perspective on Italian Pharmacovigilance Data. F1000Res 2021, 9, 1176, doi:10.12688/f1000research.26523.2.*
83. ^*Wei, Q.; Wang, P.; Yin, P. Confidence Interval Estimation for Vaccine Efficacy against COVID-19. Front Public Health 2022, 10, doi:10.3389/fpubh.2022.848120.*
84. ^*Jang, B.; Kim, H.W.; Kim, H.-S.; Park, J.Y.; Seo, H.; Kim, Y.K. Measles Virus Neutralizing Anti-body Response and Durability Two Years after One or Two Doses of Measles–Mumps–Rubella Vac-cine among Young Seronegative Healthcare Workers. Vaccines (Basel) 2022, 10, 1812, doi:10.3390/vaccines10111812.*
85. ^*Bianchi, F.P.; Mascipinto, S.; Stefanizzi, P.; De Nitto, S.; Germinario, C.; Tafuri, S. Long-Term Im-munogenicity after Measles Vaccine vs. Wild Infection: An Italian Retrospective Cohort Study. Hum Vaccin Immunother 2021, 17, 2078–2084, doi:10.1080/21645515.2020.1871296.*
86. a, b*Wang, Q.; Wang, W.; Winter, A.K.; Zhan, Z.; Ajelli, M.; Trentini, F.; Wang, L.; Li, F.; Yang, J.; Xiang, X.; et al. Long-Term Measles Antibody Profiles Following Different Vaccine Schedules in China, a Longitudinal Study. Nat Commun 2023, 14, 1746, doi:10.1038/s41467-023-37407-x.*
87. ^*Hassouneh, F.; Goldeck, D.; Pera, A.; van Heemst, D.; Slagboom, P.E.; Pawelec, G.; Solana, R. Func-tional Changes*

of T-Cell Subsets with Age and CMV Infection. Int J Mol Sci 2021, 22, 9973, doi:10.3390/ijms22189973.

88. ^*Al-Sheboul, S.A.; Brown, B.; Shboul, Y.; Fricke, I.; Imarogbe, C.; Alzoubi, K.H. An Immunological Review of SARS-CoV-2 Infection and Vaccine Serology: Innate and Adaptive Responses to MRNA, Adenovirus, Inactivated and Protein Subunit Vaccines. Vaccines (Basel) 2022, 11, 51, doi:10.3390/vaccines11010051.*
89. ^*Yokota, S.; Saito, H.; Kubota, T.; Yokosawa, N.; Amano, K.; Fujii, N. Measles Virus Suppresses In-terferon-α Signaling Pathway: Suppression of Jak1 Phosphorylation and Association of Viral Acces-sory Proteins, C and V, with Interferon-α Receptor Complex. Virology 2003, 306, 135–146, doi:10.1016/S0042-6822(02)00026-0.*
90. ^*Shaffer, J.A.; Bellini, W.J.; Rota, P.A. The C Protein of Measles Virus Inhibits the Type I Interferon Response. Virology 2003, 315, 389–397, doi:10.1016/S0042-6822(03)00537-3.*
91. ^*Shivakoti, R.; Hauer, D.; Adams, R.J.; Lin, W.-H.W.; Duprex, W.P.; de Swart, R.L.; Griffin, D.E. Limited In Vivo Production of Type I or Type III Interferon After Infection of Macaques with Vac-cine or Wild-Type Strains of Measles Virus. Journal of Interferon & Cytokine Research 2015, 35, 292–301, doi:10.1089/jir.2014.0122.*
92. ^*Torracinta, L.; Tanner, R.; Vanderslott, S. MMR Vaccine Attitude and Uptake Research in the United Kingdom: A Critical Review. Vaccines (Basel) 2021, 9, 402, doi:10.3390/vaccines9040402.*
93. ^*Esolen, L.M.; Ward, B.J.; Moench, T.R.; Griffin, D.E. Infection of Monocytes during Measles. J In-fect Dis 1993, 168, 47–52, doi:10.1093/infdis/168.1.47.*
94. ^*Sullivan, J.L.; Barry, D.W.; Lucas, S.J.; Albrecht, P. Measles Infection of Human Mononuclear Cells. I. Acute Infection of Peripheral Blood Lymphocytes and Monocytes. Journal of Experimental Medi-cine 1975, 142, 773–784, doi:10.1084/jem.142.3.773.*
95. ^*GRIFFIN, D.E.; WARD, B.J.; JAUREGUI, E.; JOHNSON, R.T.; VAISBERG, A. Natural Killer Cell Activity during Measles. Clin Exp Immunol 2008, 81, 218–224, doi:10.1111/j.1365-2249.1990.tb03321.x.*
96. ^*Garcia, M.; Pineau, A.; Guillard, O.; Ragot, S.; Lévêque, N.; Agius, G. Low Serum Selenium Concen-trations in French Patients with Measles. Curr Res Transl Med 2017, 65, 89–91, doi:10.1016/j.retram.2016.10.002.*
97. [a, b]*Avery, J.; Hoffmann, P. Selenium, Selenoproteins, and Immunity. Nutrients 2018, 10, 1203, doi:10.3390/nu10091203.*
98. ^*Solovyev, N.; Drobyshev, E.; Blume, B.; Michalke, B. Selenium at the Neural Barriers: AReview. Front Neurosci 2021, 15, doi:10.3389/fnins.2021.630016.*
99. ^*Mayo-Wilson, E.; Imdad, A.; Herzer, K.; Yakoob, M.Y.; Bhutta, Z.A. Vitamin A Supplements for Preventing Mortality, Illness, and Blindness in Children Aged under 5: Systematic Review and Meta-Analysis. BMJ 2011, 343, d5094–d5094, doi:10.1136/bmj.d5094.*
100. ^*Pezzotti, P.; Bellino, S.; Prestinaci, F.; Iacchini, S.; Lucaroni, F.; Camoni, L.; Barbieri, M.M.; Ricciardi, W.; Stefanelli, P.; Rezza, G. The Impact of Immunization Programs on 10 Vaccine Preventable Diseases in Italy: 1900–2015. Vaccine 2018, 36, 1435–1443, doi:10.1016/j.vaccine.2018.01.065.*
101. ^*de Witte, L.; Abt, M.; Schneider-Schaulies, S.; van Kooyk, Y.; Geijtenbeek, T.B.H. Measles Virus Targets DC-SIGN To Enhance Dendritic Cell Infection. J Virol 2006, 80, 3477–3486, doi:10.1128/JVI.80.7.3477-3486.2006.*
102. ^*Derakhshani, S.; Kurz, A.; Japtok, L.; Schumacher, F.; Pilgram, L.; Steinke, M.; Kleuser, B.; Sauer, M.; Schneider-Schaulies, S.; Avota, E. Measles Virus Infection Fosters Dendritic Cell Motility in a 3D Environment to Enhance*

Transmission to Target Cells in the Respiratory Epithelium. Front Im-munol 2019, 10, doi:10.3389/fimmu.2019.01294.

103. ^*Gadroen, K.; Dodd, C.N.; Masclee, G.M.C.; de Ridder, M.A.J.; Weibel, D.; Mina, M.J.; Grenfell, B.T.; Sturkenboom, M.C.J.M.; van de Vijver, D.A.M.C.; de Swart, R.L. Impact and Longevity of Measles-Associated Immune Suppression: A Matched Cohort Study Using Data from the THIN Gen-eral Practice Database in the UK. BMJ Open 2018, 8, e021465, doi:10.1136/bmjopen-2017-021465.*

104. ^*Arbore, G.; West, E.E.; Rahman, J.; Le Friec, G.; Niyonzima, N.; Pirooznia, M.; Tunc, I.; Pavlidis, P.; Powell, N.; Li, Y.; et al. Complement Receptor CD46 Co-Stimulates Optimal Human CD8+ T Cell Effector Function via Fatty Acid Metabolism. Nat Commun 2018, 9, 4186, doi:10.1038/s41467-018-06706-z.*