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Evolution of, Host Immunity to, and Vaccination against Emergent Infections

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ABSTRACT

The issue of host pathogen interactions, and how during evolution they have driven medical, sociopolitical and economic changes to society, have been crystalized globally in response to the recent SARS-CoV-2 pandemic. There is a long global history of infectious disease outbreaks, with good evidence as to the nature and efficacy of how they were handled by the affected communities. A systematic approach in the current epidemic has been less forthcoming, with many responses driven more by fear, ill-informed media hysteria, and a repeated reliance on poorly-tested treatments, many of which have, somewhat predictably, proven ineffective, further eroding confidence in governments, medicine, and science.

The overview below highlights in broad strokes those key areas which need consideration in terms of their influence on any novel infection.

1. What is the epidemiology of the infection; is it new, or a recurrence of an older (modified?) pathogen; and what factors have led to its presence now?
2. What do we know about host resistance mechanisms to infection and how they might contribute to emerging infectious disease? Are they different in different microenvironments (e.g. in humans in different organs and tissues), and do they change over time (both short-term and long-term) post exposure to pathogen?
3. Can a better understanding of resistance come from an analysis of the genetics of the infectious agent, and that of the responding host?
4. Does improved understanding of all these aspects which contribute to the origin of new infectious disease help direct application of new technologies to improving vaccination regimes to induce resistance, or develop novel pharmaceuticals directed at disease provoking agents? This review is not restricted to the current SARS-CoV-2 pandemic, although in each section highlighted below there is included a discussion pertinent to this particular pathogen.

Keywords: Emergent infections, Innate immunity, Adaptive immunity, Vaccination, Genetics of resistance

INTRODUCTION

We live in a planet where, as we hear on a daily basis, the environment and local ecology is rapidly changing. This has been argued as a prime factor in the changes in distribution and host range of many known pathogens, and the evolution of new ones [1]. A popular theme has been that many new infections arise from pathogens, previously well adapted to one species, infecting a new species to cause pathology. Alternate more controversial views, as discussed below, have also speculated on the origin of novel infections outside of this planet [2-5]. It remains a truism nevertheless, that not all individuals infected with the same pathogen develop disease, and certainly not the same intensity of disease. Understanding the nature of host resistance (immunity) is also a key to developing a consensus strategy to tackling a widespread infection, as indeed is understanding the genetic factors, both host and pathogen, which contribute to variability.

It has become apparent over the last decades with the growing realization of the problems of drug-resistant infections incurred by "man-made" selection, e.g. through antibiotic overuse, it is critical that we characterize host: pathogen interactions in detail before we can consider how

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we might develop new sustainable methods to target infectious agents. Such approaches take time. Importantly, as discussed below, the rapid introduction of novel vaccines for SARS-CoV-2 has been claimed to be a success of modern science and medicine yet there remains a concern that our detailed biological knowledge of this pathogen is so limited that such a conclusion may be quite premature, and adverse effects of current vaccine strategies may yet be revealed.

Each of these concerns is discussed in turn below with reference to epidemiology; host resistance mechanisms of disease; genetic variation in infectious agents and host resistance; and finally new strategies to improve host resistance (vaccination) and development of technologies for advanced detection of novel pathogens.

THE EPIDEMIOLOGY OF EMERGENT INFECTIOUS DISEASE

Emerging new infectious diseases and the re-emergence of those thought to be controlled and/or quiescent, have become a global issue of significant importance. Such diseases in general fall into one of two categories, namely Zoonotic diseases which are transmitted from animals to humans through direct contact or via food/water, and Vector-borne diseases. Both are major sources of mortality and morbidity globally [6]. While classically mosquito-borne viruses are typically responsible for many of the vector-borne infections, including yellow fever, chikungunya virus, and dengue virus, most emerging viral infections have a zoonotic origin, with fruit bats and flying fox species as the probable wildlife hosts [6]. Amongst those included in such a list are Hendra virus (equine morbillivirus), Menangle virus associated with porcine stillbirths and malformations, and Nipah virus, associated with pneumonia in pigs and encephalitis in humans [7]. Foremost globally amongst nonzoonotic viruses, are enterovirus 71 (a common cause of hand, foot, and mouth disease, which has also been linked with cases of encephalitis [8]), and HIV [9].

Emerging viral infections of the nervous system caused primarily by RNA viruses and associated with acute or subacute encephalitis, are also prominent amongst newer concerns, with pathology often resulting from a direct viral effect or from a host immune response against the infection. Vector-borne viruses transmitted by arthropods, or arboviruses, and responsible for epidemics with significant neurological disease, include the Zika virus epidemic in South Americas (2015), and West Nile and Dengue viruses [10]. As is discussed in more depth below, other factors implicated in an increased incidence of novel infections include altered animal migration, globalization of travel with disease importation, disruption of ecological niches with wider dispersal of mosquito vectors [1], and novel and increased cross-species contact. All have been linked to or assumed to be re-emergence of "old viruses" often with a different pathophysiology, as may be the case for Ebola virus [10,11].

The argument has been made that one of the major factors in the increased burden of emerging infections are an expansion of ecotourism-based industries, altered land-use practices, and the competition for limited resources which has led to increased contact between free-ranging wildlife and humans. This has led to health risks to both humans and wild-life alike through bilateral exposure to novel pathogens [10]. An extensive survey of infections has been reported with *Mycobacterium tuberculosis*, a human pathogen, in free-ranging animals in the African continent, along with discussion of the role permanent reservoirs of *Mycobacteria species* in both domesticated and captive/free-ranging wildlife may play in limiting success on TB eradication programs, as well, as contributing a significant public health threat [10-12].

Non-tuberculous mycobacteria, and particularly those of the *Mycobacterium avium* complex (MAC), also represent a significant public health threat [12]. These organisms are found ubiquitously in soil and water worldwide. Members of MAC cause an array of infections in both humans and animals that can be multidrug resistant, and can cause death, particularly MAC lung disease which is now more prevalent than tuberculosis in many countries, including the United States. In a recent review Keen [12] used comparative genomics to clarify MAC biology, characterizing distinct genes for virulence and antibiotic resistance in isolates from different sources, and highlighting the concern regarding rapid evolution of novel pathogenic sub-strains [12]. The problems caused by evolution of multidrug resistant bacteria is nowhere better highlighted than in the clinical concerns raised by the now widespread dispersion of methicillin-resistant *Staphylococcus Aureus* (MRSA). This has been ably discussed in one pocket of infection (in Rio de Janeiro) which was caused by an emerging sub-lineage with marked resistance to monocyte phagocytosis [13]. Another common pathogen which has come under intense scrutiny with evidence of emerging increased pathogenicity is Candida. Candida species represent opportunistic fungal pathogens which form a part of the normal skin and mucosal microflora. Their overgrowth can cause life-threatening invasive infection most prominently in immunocompromised patients, while in healthy immunocompetent subjects generally a vigorous innate immune response ensures that no or minimal (oral thrush) infections occur. Emergence of Candida strains with molecular strategies to evade host attack by proteolysis of components of the immune system and/or by interfering with immune signaling pathways, along with others that are resistant to current antifungal agents, has again led to concern [14]-see also discussion in [2] and [15].

Conventional dogma stresses that disease emergence generally "reflects dynamic balances and imbalances, within

complex globally distributed ecosystems comprising humans, animals, pathogens, and the environment" and that "understanding these variables is a necessary step in controlling future devastating disease emergences" [16,17]. We have argued elsewhere that there are other variables, not considered to date, which have likely contributed in no small manner to the widespread dispersion of the current SARS-CoV-2 pandemic, and they may also help explain other viral pandemics occurring over the last several decades [2-5,18]. A recent review of the more conventional arguments summarizes how Coronaviruses, a major cause of respiratory disease in animals, have been shown to be constantly evolving, crossing host species barriers, and expanding their host range. Novel coronaviruses have emerged in humans and domestic animals, as well as in captive wildlife or wild populations, raising the concern that evolution and emergence of novel viruses might be enabled by frequent cross-species transmission or zoonosis. Thus a recent review compared across several mammalian host species the current knowledge of host range and any exceptional circumstances reported in cases of putative cross-species transmission events of emerging coronaviruses in humans and common domestic mammals [19], concluding that all coronaviruses considered had similar host ranges and were closely related, suggestive of recent rapid diversification and spread. Their emergence was associated with high-host-density environments which could have facilitated multi-species interactions (e.g., shelters, farms, and markets), all features consistent with the hypothesis of cross species infection/evolution of a novel disease. Compelling molecular and biological arguments suggesting that this is not a likely explanation for the current pandemic are reviewed in detail elsewhere by Steele [20] and Lindley & Steele [21], with further clarification below.

IMMUNE MECHANISMS IMPLICATED IN VARIABILITY IN RESISTANCE TO INFECTION

The immune system is comprised of both an innate host defense system and an acquired one. The former, activated within hours of pathogen contact, is present even in non-vertebrates, and is thus often regarded as a more "primitive" host resistance mechanism. Exquisite specificity, or the ability to discriminate between multiple different foreign insults by individual cells, is much more limited within the innate immune system than in the acquired immune system (lymphocyte based). It is nevertheless worthy of note that a variety of anti-viral genes (> 1000) are activated on pathogen entry into eukaryotic cells. These in turn encode molecules targeting multiple generic features of the viral life cycle (of which the AID/APOBEC and ADAR deaminases are only a small component of what can be considered an 'innately reactive anti-viral wall of responses see [21-23].

In the acquired immune response, clonal expansion of individual T and B lymphocytes, each using a complex gene splicing event during cell development, occurs following pathogen exposure to produce cells with a lymphocyte receptor recognition repertoire essentially capable of recognizing an almost infinite number of new determinants on novel pathogens [24]. These cells undergo further differentiation events days to weeks after pathogen contact, to produce specific effector cells with unique biochemical pathways designed to eradicate specific pathogens (production of antibodies by progeny of B lymphocytes; display of "killer pathways" by activated effector T cells). Following successful eradication of pathogens, cells of the acquired immune system alter their differentiation pathways to generate "long-lived specific memory cells", retaining a specific memory of past experience and able to expand in numbers rapidly to combat any recurrence of the same pathogen, even many years after primary infection. Cells of the innate immune system use a more restricted pathogen pattern recognition repertoire (PRR) to detect foreign material/pathogens displaying redundant determinants recognized by those PRRs [25,26]. While pathogen-specific "memory" was thought not to exist in cells of the innate immune system, it has become apparent over the past 1-2 decades that at least in vertebrates, a mechanism akin to "kindling in neuronal pathways" leads to a faster re-activation of innate immune mechanisms after repeat contact with the same or similar pathogen [27].

For a viral infectious agent, virus entry, namely attachment to and penetration into the host target cell, is the first step of the virus life cycle which governs successful virus emergence in any host population. This is reflected in the development of antiviral vaccines, most of which aim to induce neutralizing antibodies to prevent virus entry into cells. Anti-hemagglutinin IgG (for influenza virus), and antibodies targeting the cell surface receptor angiotensin-converting enzyme 2 (ACE2), as well those enhancing the cleavage effect of type-II trans membrane serine protease (TMPRSS2) on the (viral attachment) S protein for SARS-CoV-2, are examples of this [28,29]. However, other natural immune defenses are present within cells, known as intrinsic immunity mechanisms [30] which also interfere with virus entry. Interferon-induced trans membrane (IFITM) proteins, which inhibit fusion between viral and cellular membranes, were the first well described factors which restricted virus entry. Now multiple other host factors with antiviral potential have been described [30], including amongst others lymphocyte antigen 6E (LY6E), nuclear receptor co-activator protein 7 (NCOA7), and others, though their role(s) in any particular infection remains to be elucidated [30].

In a recent article we reviewed in some detail the nature of innate immune mechanisms activated in response to viral infections [31]. These involve type I and type III interferon response pathways [27]. [Note that there is considerable heterogeneity in the interferons themselves, and this alone can contribute to pathology. This is well documented in a recent report on Chikungunya virus infection, where it now seems that only IFN, and not IFN (both type I IFNs) is

responsible for control of chronicity and viral persistence [32]]. These IFNs in turn activate cellular AID/APOBEC and ADAR deaminases inducing mutagenesis of the pathogen genome by extensively mutating their genomes with C-to-U (T) and A-to-I(G) mutations [21,33-35]. The afore-mentioned "training" of innate immunity involves epigenetic changes (altered DNA methylation; histone deacetylase activity) which results in more rapid activation of the genes implicated in response to pathogens [36]. Training of innate immune responses helps explain why infant mortality, and even adult mortality, is less in BCG vaccinated cohorts (BCG admixed with adjuvants is an excellent inducer of innate immune responses) than in non-vaccinated cohorts from the same population [37]. In comparison, it is thought that defects in both rapid-response innate immunity along with defects in acquired immunity, both of which are evident in the elderly, may be responsible for their increased morbidity/mortality following viral infection [38-40].

Innate immunity is relevant too in HIV-1 infection. A compromised acquired immune system, following viral mediated destruction of (T) lymphocytes, and in particular the CD4/CD8 ratio with CD4 lymphopenia, is well recognized as a cause of pathogenesis [9]. However, the innate immune system at mucosal surfaces also plays a key role in viral eradication, including complement, dendritic cells (DCs), macrophages, and NK cells as well as cytokines and chemokines The interplay between the host response and the viral evolution to evade this, involving RNA-mediated rapid mutations, pathogen-associated molecular patterns (PAMPs) modification, and attenuation of NK cell activity and complement receptors, is thought to contribute to the outcome of HIV-1 infection at mucosal barriers [41]. There is a need to understand/classify the pathogenesis of any emerging (viral) infection in order to prevent and reduce transmission and begin to develop rationale therapeutic approaches to treatment [42]. In a recent study describing events following HIV-1 and EBOLA viral binding and entry into dendritic cells, even induction of type 1 interferons on DCs seemed to represent a double-edged sword in virus control [43]. Siglec-1, a sialic acid-binding type I lectin receptor, is upregulated by type I interferons on DCs. Enveloped viruses including HIV1 and Ebola virus, incorporate sialic acid-containing gangliosides on their viral membrane enabling recognition by Siglec-1. The subsequent enhanced DC infection thus contributes, following DC migration, to viral spread throughout local tissues.

There is a plethora of data exploring the role of acquired immune responses to viral and other microbial pathogens, and since many of these agents encounter their hosts initially at mucosal surfaces, it is not surprising that studies of mucosal immunity (as well as innate immunity-see HIV above) have featured prominently. Conventional dogma is that activated T lymphocytes are crucial for protective immunity to viral infections, a feature consistent with what we understand about the quite different antigen recognition by B versus T cells. The latter recognize cell surface MHC-presented epitopes altered following viral infection, and thus destroy potential "viral factories" before viral replication is completed within the infected cell. In contrast, B cell derived immunoglobulin recognizes the topography of the foreign determinants on pathogens, which explains the importance of neutralizing Ig in preventing pathogen binding and entry to cells (see above). Ig also represents an important host defense against organisms (bacteria) which exist outside of cells. Coating these with Ig renders them recognizable by the (enzymatic) factors in the complement cascade, and also for opsonization by cells with their own receptors for a region (Fc) of Ig.

It is important to appreciate that while monitoring of (serum) Ig may make for easier assessment of development of an immune response to a pathogen, it may not necessarily provide useful information about the development of protective immunity in the infected host, particularly if this is mediated by T cell or innate immunity, or by secretory IgA at the mucosal surface (only the 7S monomer is in blood plasm/serum). Mucosal dimeric (11S) secretory IgA, with four antigen binding sites arranged as a V-shaped molecule connected at the base of the alpha chain constant regions by a J chain, is both non-complement fixing (and thus a putative Ab-mediated enhancement blocker) and is highly avid. Such a molecule is perfectly suited for very strong and effective neutralization of toxins, viruses, and putative intracellular pathogens before they bind to mucosal cell surfaces during respiratory virus infections. In general serum antibody responses correlate poorly with disease for mild infections. More robust responses reflect more severe or persistent/recurrent exposure. In contrast, virus-reactive T-cell immunity lasts longer.

This importance of attention to the route of infection in understanding host immunity to infection is highlighted with the recent SARS-CoV-2 pandemic. This virus primarily gains entry to the host through the upper airway, yet data focused on immunity at the local mucosal surfaces is limited [21,31]. The nasopharyngeal-associated lymphoid tissue (NALT) is a component of the mucosa-associated lymphoid tissue (MALT), known to be the largest component of the entire immune system. Crucial components of the airway mucosal immune system are secretory IgA (S-IgA) along with tissue-resident T and B cells, so-called mucosa-associated invariant T (MAIT) cells and innate immune components, including complement and mucosal interferons (IFNs). After SARS-CO-V2 infection mucosal S-IgA as well as systemic IgG antibody responses are induced [44], with neutralizing activity of IgA polymers in the nasopharynx far exceeding (7-15fold) that of IgA monomers or serum IgG [45], consistent with our prior understanding of mucosal immunity. SARS-CoV-2 patients with gastrointestinal symptoms fared better (lower death rate) than patients without GI symptoms, and intestinal pools of virus were

detected (likely ongoing MALT stimulation) at > 3months following overt upper airway disease [46]. Studies of paired respiratory wash and blood samples of memory T cells showed detectable activity in NALT unrelated to activity in serum derived cells, again reflective of the importance of a tissue compartmentalization of the immune system, and the likely importance of MALT in a protective SARS-CoV-2 immune response [47]. Importantly, however, in some SARS-CoV-2 infected individuals there is impairment both systemically and mucosally, of the type I IFN innate immune response which can be rectified by mucosally administered recombinant type I-IFN, with excellent effects on recovery in infected patients [48].

Other host resistance mechanism(s) exist preventing uncontrolled inflammation, in vascular tissue [49] which can be disrupted by infectious agents. A superfamily of endogenous chemical molecules (chemokines) participate in the resolution of inflammation, with MCPIP-1 (Regnase-1), the best-studied member [50], being an endonuclease which controls the stability of mRNA and microRNA (miRNA), in turn resolving inflammation and promoting viral clearance.

GENETIC FACTORS CONTROLLING IMMUNOBIOLOGY OF RESISTANCE TO INFECTION

Polymorphisms in several immune response genes results in heterogeneity in natural and induced (by vaccines) immune responses to many pathogens [51]. Nevertheless, the public-health paradigm of population-based infectious disease vaccinology has led to eradication of many diseases, including smallpox, and control of others including measles/mumps/rubella/varicella/polio, with a high cost-benefit ration across global societies. Important genetic differences (e.g. humans HLA Class II controlling human antibody responses) can contribute to different responses to Hepatitis B virus (HBV) and measles virus vaccines [52-57] with increased susceptibility to HBV in some populations. In the case of susceptibility to SARS-CoV-2, clear inborn genetic errors in innate immune anti-viral immunity are implicated in some vulnerable patients [58]. There are sex-related differences in response to vaccines, with, in general, women mounting an increased antibody response over men [59]. Subtle racial/ethnic differences such as the Km/Gm antibody carried by Native Alaskans and Native Americans were hypothesized to lead to impaired immune response to polysaccharide vaccine antigens [60,61].

Another important HLA-linked polymorphism in infection-related susceptibility has recently come to light with regard to a novel antiviral activity in the major histocompatibility complex (MHC) class II transactivator (CIITA) for Ebola virus [62]. CIITA is thought to induce resistance by activating expression of an isoform (p41) of the invariant chain CD74, which inhibits viral entry by blocking cathepsin-mediated processing of the Ebola glycoprotein. It is now evident that the CD74 p41 also blocks the endosomal entry pathway of multiple coronaviruses, including SARS-CoV-2., implying that CIITA and CD74 have a hitherto unappreciated role in host defense against a range of viruses, far beyond their accepted roles in regulation of antigen presentation. Similarly it has recently been reported that T-cell immunoglobulin (Ig) and mucin domain (TIM) proteins play an unexpected but critical role in viral infection, inhibiting both Ebola virus and HIV-1 release from infected cells, and resulting in diminished viral production and replication [63]. Expression of TIM-1 was shown to cause HIV-1 Gag and mature viral particles to accumulate on the plasma membrane, a function of the phosphatidylserine (PS) binding sites of TIM-1. In support of these findings, knockdown of TIM-3 in differentiated monocyte-derived macrophages enhanced HIV-1 production.

Not only HLA-related polymorphisms, which control recognition of antigenic epitopes on the infectious pathogen, but also cytokine gene polymorphisms are associated with regulation of immunity to infectious agents [51, 58, 64]. As noted, above gender differences have been reported for viral immunity [59, 65, 66] -see [67] for a review of sex related difference in immunity. Given both qualitative and quantitative changes in immunity with age, with a marked shrinkage in the immune response (T cell) repertoire [68] and expansion of “exhausted T cells with high PD-1 expression [69] during aging, wide variations in response to both natural infection and vaccination with age are unsurprising [40].

Original antigenic sin (OAS [70]) describes the phenomenon whereby the shape of the ongoing immune response to a persistent/recurrent pathogen is “molded” by the initial response made. Thus most influenza virus antibodies in a population show cross-reactivity to the original (pioneer) strain for that group [71-74]. In general neonatal immune responses are less heterogeneous than in adults’ counterpart, contributing to the poor response to vaccination in neonates particularly when using recombinant antigen (not inactivated viral) vaccines. Immunity generated by live virus infection produces a superior response in neonates presumably reflecting the much broader epitope range of immune challenge. The decline in the immune repertoire with age, and thus less efficacious vaccination, is discussed above. “Imprinting” (how first exposure to a pathogen shapes subsequent exposures) [73,74], and “interference” (how antibody to an original strain of pathogen interferes with subsequent immune responses to different strains), compounds these age related altered immune responses to pathogens. Given these observations, some data uncovered in regards to a recently described variant of SARS-CoV-2, omicron, with a high number of mutations in key epitopes of neutralizing antibodies on the viral spike glycoprotein suggesting a capacity for immune evasion, is worthy of note. Convalescent and vaccinated individuals showed little serum neutralizing activity to this variant, yet further boosting with mRNA vaccines led to marked increase in serum

neutralizing activity to omicron. The authors speculated this may represent an effect of booster-induced conventional affinity maturation of the Ig response in such individuals [75]. However, it is important to note that there is little evidence that serum IgG is an important clinical marker of vaccine efficacy (see also below), though vaccination does seem to reduce disease severity. This may be why, following evolution of novel variants, further vaccination can improve clinical efficacy, through booster of an unmeasured, non-serum IgG response.

A frequently used approach to understanding the genetics of host resistance to pathogens comes from analysis of "experiments of nature" (susceptibility in natural genetic variants [57, 58, 60,61]) or deliberate experimentation. For *M tuberculosis*, for instance, immunocompromised individuals have increased susceptibility to tuberculosis, consistent with studies which indicate that T cell-mediated immunity plays a critical role in resistance [76,77]. Interferon gamma (IFN) is a principal mediator of macrophage activation and resistance to intracellular pathogens, and indeed mice with a targeted disruption of the IFN gene fail to produce reactive nitrogen intermediates, cannot restrict growth of the bacilli, and succumb to tuberculosis. Death is delayed but not prevented by treatment with exogenous IFN [76]. Independent human studies confirm the risk associated with defective IFN production [77].

Influenza, causing some 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths per year world-wide [78], is a disease for which vaccination is the mainstay of protection, although ongoing annual update of vaccines is needed to account for antigenic drift in the pathogen resulting in escape from earlier (effective) immunity. Vaccine efficacy is conventionally followed using influenza serum hemagglutination antibody titers, where a pre-determined increase in titer: e.g. >40 in 18–60-year-olds with a 4-fold increase in titer post vaccination and >40% seroconversion in the same group, is historically associated with ~50% reduction in influenza risk [79], consistent with data on the importance of anti-HA titers in recovery after natural infection [78]. This may not be the case in the elderly [80], where monitoring of cell mediated immune responses and mucosal secretory IgA (dimeric) may be more valid predictors of efficacy [31,44,45,80-83]. In the absence of use of live vaccines, or a live attenuated virus vaccine it is important that the recombinant material included in any vaccine covers the antigenic determinants inducing the relevant immune response (T and/or B cell mediated) in the population at risk [84-86]. Indeed, extensive work and analysis over the past 50 years on the alternate feedback and reciprocal control between cell mediated and humoral immunities viz. Th1 (cell mediated induction of IFN etc.) and Th2 (largely enhanced humoral IgG1/IgG2, IL-4, IL10 immune reactions), summarized elsewhere [87-90], indicates that induction of T or B cell immunity itself is open to modification. This has generated investigation of whether vaccinations strategies inducing T and/or B cell immunity (including for SARS-CoV-2) might be optimal to induce resistance (see below and [91]).

Successful pathogens have evolved multiple strategies to survive and persist within host cells. The panoply of bacterial effector molecules which enable bacteria both to enter the host cell and manipulate host gene expression to circumvent clearance by the host immune response are described in some detail by Denzer [92]. Similarly, Demeure and colleagues [93] have reviewed the virulence factors, and their functions, which play roles in the ability of *Y. Pestis* to subvert the mammalian innate immune response to cause pneumonic plague diagnosis. The same genomic correlative approach has been used to understand resistance/susceptibility to viral infections, including Zika, vaccine and dengue viruses. Arboviruses are thought to maintain a high mutation rates related to the proofreading ability of their viral polymerases, thus facilitating adaptive evolution and emergence. It is known that in general, when assessed experimentally *in vitro*, viral replicas have a high fidelity with faithful replication of host cell AID/APOBEC and ADAR generated errors (C>U, A>I) in the viral genomes during innate immune response (see [94-97]).

The emergence of the Zika virus infection in 2013-2014 was associated with an envelope protein V473M substitution which increased neurovirulence, maternal-to-fetal transmission, and viremia all of which culminated in rapid urban transmission- a similar artificially engineered strain also increased neurovirulence in neonatal mice and produced higher viral loads in the placenta and fetal heads in pregnant animals [98]. Studies of different vaccinia strains, in particular a highly attenuated and non-replicative strain, and a virulent wild-type (WT) strain, showed that macrophage/monocyte and $CD4^+$ T cell responses to virus were decreased in mice infected with WT stains, with T cells showing decreased expression of co-stimulatory molecules and production of cytokines, including tumor necrosis factor alpha (TNFα), gamma interferon (IFNγ), interleukin-4 (IL-4), and IL-10, while animals infected with a non-virulent strain showed robust immunity in all cell types [99]. Similar studies in animals infected with different isolates of dengue virus showed that mice infected with isolates with the highest replicative efficiency for human or mosquito cells in vitro had the highest mortality, and non-structural proteins from such isolates caused greatest suppression of host interferon signaling [100].

Before concluding this section (below) with a review of genetic susceptibility to SARS-COV-2, it is worth recalling the previous discussions (above) of mucosal immunity, and the manner in which secretory IgA (SIgA), which is released to mucosal surfaces, may act beyond any direct function in host defense. It has been suggested that in addition to the direct function it may also contribute to the shaping of

resident microbial communities by mediating exclusion/inclusion of respective microbes and regulating bacterial gene expression-in other words, to regulating the host microbiome [101]. A recent report on this function has been published, and also serves to include a discussion of the relevance of imbalances in the Th17: Treg ratio to the SIgA axis [46] - the Th17: Treg ratio is known to be associated with gut microbiome dysbiosis and many chronic inflammatory conditions [102]. By examining the impact of Th17: Treg ratios on the IgA-microbiome in diabetic individuals (the prototype inflammatory condition considered in this study [102]) a relationship between Th17:Treg ratios, sIGA and diversity in the stool IgA-microbiome was seen. The relationship between pathogens and immunity at mucosal surfaces must thus take into account also the interaction with the pre-existing mucosal microbiome in that environment and how that affects host responses and inflammation. Highly pertinent to this issue, is the recent study of sIgA responses in immunity to SARS-CoV-2 by Cervia [103]. These authors reported that serum antibody production (IgG) against SARS-CoV-2 was most generally detected in patients with severe COVID-19, and very high IgA titers were seen in patients who developed severe acute respiratory distress syndrome. In contrast, mild disease was associated with only a transient (and reduced level of) production of SARS-CoV-2-specific antibodies but did stimulate mucosal SARS-CoV-2-specific IgA secretion. The possible role of induction of Tregs and other immune cell activation as a contributory explanation to this phenomenon is unknown.

Given the discussions above concerning the nature of immunity to SARS-CoV-2, it is not surprising that multiple genetic susceptibilities exist for this pathogen, both naturally acquired and following vaccination. Both SARS-CoV-1 and SARS-CoV-2 utilize human angiotensin-converting enzyme 2 (ACE2) as the receptor (binding to SARS-CoV spike protein) to enter cells, and several genetic variants in spike protein binding are reflected in altered susceptibility to SARS-CoV-2 infection [104]. Decreased binding in nasal cells from pediatric patients [105], may help explain their decreased infection rate. Studies of the mechanism of action of protective receptor-binding-domain (RBD) neutralizing antibodies, which either block binding, or a downstream pathway after initial binding, leading to protection are consistent with these findings [106]. Exhaustive review of RBD binding has fostered a greater understanding of novel viral "escape mutants" which have emerged as the time of viral exposure in the global population has lengthened, an understanding which will be key to improving future vaccination strategies [107].

Interestingly, a large-scale study of evidence for sero-conversion (to anti-SARS-CoV-2 antibody positive) following natural infection in Denmark found that significantly lower seroconversion was seen in individuals with BMI>30 and also those without clinically significant or low grade infection [108]. It is suggested elsewhere that a rapid innate immune response may be responsible for clearing viral infection before development of an acquired immune response in such individuals [31]. A recent study (albeit based to date only on *in vitro* findings) has also suggested an independent novel mechanism by which SARS-CoV-2 can circumvent at least acquired (adaptive) immunity, involving a spike protein mediated inhibition of DNA damage repair [109]. This is dependent upon spike protein interference with recruitment of DNA repair proteins BRCA1 and 53BP1 to site of DNA damage site. As noted in section 2. Above, effective V(D)J recombination is a crucial step in development of an acquired immune response. If this mechanism of action is upheld, it may have implications for potential side effects of full-length spike-based vaccines. In contrast, another study (from Brazil) which attempted to identify by whole-exome sequencing genetic factors involved in immune response in symptomatic COVID-19 as compared to asymptomatic exposed individuals, who were nevertheless co-habiting partners of the symptomatic individuals (83 couples studied), concluded that among the genes related to immune modulation, variants in *MICA* and *MICB*, quantitative differences in which molecules are thought to modulate natural killer (NK) activity were associated with symptomatic infections [110]. The authors suggest that a contributory factor in susceptibility to infection was a down regulation of NK cell cytotoxic activity by SARS-CoV-2 in infected individuals but not in asymptomatic partners.

DEVELOPMENT OF NEW TOOLS TO PROMOTE RESISTANCE TO EMERGING INFECTIONS

In this concluding section consideration will be given to both new and old(er) ways to combat pathogen insult. The latter in particular stresses vaccination regimes, but as has become clear during the recent SARS-CoV-2 pandemic, there are novel strategies now emerging even for vaccination technology. It should be remembered, however, that although some success has been claimed for their efficacy in the last year, we are still very much "in the dark" concerning longer-term effects, both wanted and unwanted, of such strategies.

In a world in which overuse of antibiotics has heralded an alarming increase in selection of antibiotic resistant bacterial pathogens (e.g. MRSA mentioned above, [13]), suitable alternatives to antibiotics to control bacteria have been investigated, including the use of bacteriophages. The biodiversity of phages makes these an attractive consideration for treatment of a myriad of bacterial infections [111]. Of particular interest is the notion of mixing different phages ("generalists" and more bacteria specific phages) together in cocktails, to increase the probability of killing target pathogenic bacteria without having to consider pre-screening strategies (of pathogens) for their phage susceptibility. There remains, however, the

concern that bacteriophage viruses can also evolve, including from an evolutionary specialized to a more generalized host-use, which may have unwanted effects in targeting commensal bacteria in normal micro biomes.

A more conventional approach for protection from pathogens is deliberate vaccination. In the past the focus was on use of live attenuated or whole cell vaccines, known to contain inbuilt "adjuvants" (e.g. bacterial cell wall components; other genetic material including polynucleotides) which promote auxiliary non-specific immune stimulation. The field of vaccination itself has been transformed with the use of purer (recombinant) antigens for safer vaccines, and with this there has flourished a development of novel but safe adjuvants, which both improve the efficacy of these newer recombinant vaccines, and may even be selected on the basis of their preferential ability to promote antibody or cellular immunity ([112,113]-see also [89]). Note, however, that even recombinant vaccines must be tested for safety, generally over years in studies with hundreds of thousands of patients of different ages/sex and other morbidities.

One focus of adjuvanticity is the possibility of rapid engagement of the innate immune system, which, as was discussed earlier, can evidently be trained to produce an enhanced protection from reinfection (with the same pathogen) and even enhanced immunity to novel pathogens [27]. Activation of innate immunity may in part at least be responsible for the observations that infant mortality, and even adult mortality, is less in BCG vaccinated cohorts that in non-vaccinated cohorts from the same population [36,37]. This represents the underlying principle behind the ACTIVATE trial in elderly volunteers to assess the contribution of BCG vaccine in decreasing susceptibility to bacterial disease [114].

Other novel approaches have suggested engagement of natural lipid peroxidation pathways in regulating infectious pathways and host resistance [115]. Polyunsaturated fatty acids (PUFA) are a major target of oxygenation either as natural membranous phospholipids or when released as mediators by phospholipases. An iron- and lipid peroxidation-dependent cell necrosis pathway has been characterized, referred to as ferroptosis, which involves the accumulation of peroxidized PUFA-containing phospholipids. This accumulation has been reported to have profound effects on a number of (physio)-pathological processes, including cancer, neurodegenerative and metabolic diseases, and more recently on infection and host resistance to infection. Perhaps unsurprisingly, it now seems that some microbial virulence factors can attenuate ferroptosis regulatory pathways as a means of evasion of host resistance [115].

As discussed earlier, vaccination strategies have been the mainstay of control of the incidence of infectious diseases globally, but the emergence of new viruses with the potential to cause pandemics of which SARS-CoV-2 represents but one pathogen can have a vast global impact. Vaccine technologies were designed to produce billions of doses in a short duration, with broad protection against emerging and re-emerging infectious diseases. Scientific knowledge of the molecular biology and immunology of adenoviruses (Ad) has in the past favored Ad vectors as platforms for vaccine design, inducing both humoral and cell-mediated immune responses which meet global demand. This underlies the conventional approach to developing vaccines to respiratory viruses, including coronaviruses, influenza viruses and respiratory syncytial viruses [116]. Novel, hitherto untried (in humans) vaccine strategies were recently developed to deal with the SARS-CoV-2 pandemic, using synthetic mRNA strands encoding the SARS-CoV-2-S glycoprotein, packaged in lipid nanoparticles to deliver mRNA to cells [117]. Use of a nucleoside-modified mRNA approach delivers higher maximal tolerable S-protein doses and might in part explain why these mRNA vaccines induce faster antibody responses [117]. It is worth noting, however, that two similar (nucleoside-modified) mRNA vaccines elicit quite different S-specific $CD8^+$T cell responses, which to date remains unexplained. More in-depth knowledge on the *in vivo* delivery efficiency, and the particular innate immune effects of the different mRNA vaccines, are needed to improve the understanding, design and efficacy of mRNA vaccines in the future. While there is evidence that the current SARS-CoV-2 vaccines have reduced severity and hospitalizations, particularly in the most vulnerable cohorts [118], their long-term safety, particularly in relation to e.g. autoimmune disease related phenomena, are unknown [119-124]. It is still unclear whether T and/or B cell immunity should be targeted for optimal protection. A recent article describing preliminary studies of a novel SARS-CoV-2 vaccine aimed at targeted induction of long-lived T cell immunity suggested this may be a superior mechanism of providing long-term protection. Another approach involves the concept of production of a universal vaccine [126-127]. This approach suggests the most efficacious way to tackle changes of viral epitopes targeted by the vaccine, in concert with the often suboptimal immunogenicity of current immunization strategies, is best remedied by targeting the immune response to conserved viral epitopes, along with the use of novel adjuvants and vaccination platforms.

Throughout this review, we have focused on conventional understanding of the epidemiology of most emerging infectious diseases (see section Introduction above). A major concern in the recent SARS-CoV-2 pandemic was and remains the controversy regarding our understanding of the mechanisms of initiation and spread of the disease. Current dogma still holds that person-to-person spread, including by aerosols, is predominant, though there are contradictory data which refute this. A more radical concept, which is nevertheless consistent with all the global data accumulated on this pandemic, suggests an origin in the arrival of living

systems from space, known as Panspermia (viruses, microorganisms and their spores) with an inciting event which may have originated in a cloud of dust of cosmic origin containing a pure culture of the virus arriving in large quantity first over China, and then dispersed through stratospheric transport processes following prevailing atmospheric drift [128-133]. The "fall-out" of viruses associated with SARS-CoV-2 would represent only a small perturbation of the billions of viruses per square meter per day which fall through the atmosphere. Some of these are recycled from Earth sources, but many were predicted and discussed in the past by Hoyle and Wickramasinghe [132, 133].

Assume then that emerging infectious disease may occur as an "in fall event" from the stratosphere. There has been confirmed detection of pathogens at heights up to 42km [134,135], and indeed on the exterior of the ISS orbiting the earth at over 400Km. Independent measures of the downward flux of viruses in the Sierra Nevada Mountains have ranged from $0.25x10^9$ to greater than $7x10^{10}m^{-2}$/day, numbers which are not easily explained as having originated on the ground [136-138]. We can now generate testable scientific predictions, including a pro-active rather than a reactive approach to vaccination strategy. If infectious material is accessible in the stratosphere before falling to earth, sampling of this material would provide advance warning (by 1-2 years) of new "emerging" pathogens on earth, allowing lead-time to investigate responses to infection and the development of containment/vaccination [139].

SUMMARY

This review has attempted to draw together our current state of knowledge both of the etiology of emerging pathogens; the nature of host resistance to them, and how this is a function of host genetics and immune resistance; and the changing face of how we are challenged to develop rapidly novel responses with the efficacy and variety to combat a similarly evolving pathogen resistance to host immunity. The importance of this is highlighted throughout with attention to the ongoing SARS-CoV-2 pandemic, which identifies both our limitations, but also offers hope for the future of innovative technologies. It seems self-evident that by keeping an open scientific mind and broad perspective on all aspects of the interaction of pathogens with their hosts, there is hope that errors of the past, both of omission and commission, will not spell doom for our future [140,141].

DECLARATIONS

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