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Perspective

A Stepwise Infection and Immunity Strategies to Prevent and Treat an Emerging Infection

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Abstract

Global warming, transportation and urbanization expose humans to novel pathogens for emerging infections arising from microbial mutation, vector-borne and/or zoonotic transmission. We have experienced and studied immunopathogenesis of 4 emerging infections including enterovirus 71 encephalitis, dengue hemorrhagic fever, severe acute respiratory syndrome (SARS), and novel influenza A(H1N1) in the past 2 decades. Based on our studies and references from literature, here, we have summarized a stepwise infection and immunity regimens to prevent and treat an emerging infection. A consensus to monitor virus-host-environment interactions in the global village is the most important thing, particularly the potential mutants of emerging RNA viruses and herd immunity of risk populations, poultries, vectors and wild animals. In this article, we provide a stepwise infection and immunity strategies to make an emerging infection preventable and treatable by monitoring virus-host-environment interactions, developing vaccines, anti-virus agents and/or immunotherapies.

Environmental Evolution of Emerging Infections

Changes of global ecology, e.g. global warming, transportation and urbanization, expose humans to novel pathogens for emerging infections arising from microbial mutation, vector-borne and/or zoonotic transmission. Most of the common emerging infections are mediated by RNA viruses which pose a higher rate of genetic mutation, sequence deletion, recombination and reassortment of RNA virus codes [1-3]. Severe acute respiratory syndrome (SARS), avian flu and seasonal flu are known to emerge from sequence mutation, deletion, recombination and/or reassortment of RNA segments. Vector-borne diseases such as yellow fever, dengue hemorrhagic fever and West Nile virus encephalitis are transmitted by mosquitos and affected by weather and global warming [4,5]. Zoonotic diseases: Ebola, Lassa and Hantavirus infections are affected by urbanization, migration of animals and social culture [6,7].

Host Immunity and Herd Immunity for Emerging Infections

Host individual immunity and herd immunity determine the transmission and reproduction number (Ro) of an emerging infection. Individual immunity is largely influenced by age, genetic inheritance and comorbidities. For instances, it is known that elders with comorbidities have a higher fatality in the outbreaks of seasonal flu and SARS (SARS-CoV-1, SARS-CoV-2 and MERS-CoV) [8-10]. Genetic variants in IL6R, TLR3, and DC-SIGN genes were associated with susceptibility and/or severity of dengue fever (DF) [11]. We have found that CD209 genotypes are significantly associated with the susceptibility of DHF [12]. TLR7 genetic variants cause predisposition to severe COVID-19 infections [13]. Interferon-inducible transmembrane protein 3 (IFITM3) gene are associated with susceptibility to and protection of severe influenza [14,15]. Herd immunity is another key factor that determines the transmission on endemic or epidemic spread of an emerging infection. Each year, human seasonal flu emerges with certain serotype of a mutant with antigen drift resulting in endemic or epidemic of influenza depending on herd immunity and coverage of population immunization. The seasonal flu endemic or epidemic is usually occurring in autumn and winter while humans live in an atmosphere with a shorter social distance, lower temperature and humidity [16]. Based on the equation (1-1/Ro x 100%) to

control an infection calculated by a reproduction number, Ro, to cease an epidemic of seasonal flu requires a herd immunity or coverage of population vaccination over 20% population (1-1/Ro = 1-1/1.25=20%) while the seasonal flu has a Ro value between 1.2 and 1.3. The Ro value for SARS-CoV-2 is estimated at 2.3 [17], whose control of the pandemic requires the population herd immunity or mass vaccination over 57% (1-1/2.3 x100%= 57%).

A Total Solution of Infection and Immunity Regimens for Preventing an Emerging Infection

We have experienced and studied immunopathogenesis of 4 emerging infections including enterovirus 71 encephalitis [18-20], dengue hemorrhagic fever [21-23], severe acute respiratory syndrome (SARS) [24-26], and novel influenza A(H1N1) [27-29] in the past 2 decades. Based on our studies and references from literature, here, we have summarized a stepwise infection and immunity regimens to prevent and treat an emerging infection by 10 sequential steps for infection and immunity control below:

Monitor of mutant viruses, herd immunity and vectors. Infection immunity of an emerging infectious disease is determined by virus-host-environment interactions. Emerging infections are frequently derived from RNA viruses which usually lack a 3-exonuclease that is present in DNA-dependent polymerases providing proofreading ability for the genome stability during replication [30]. Global warming, extreme climate and global transportation have promoted the widespread of the vector-born transmitted diseases to different regions of the world [31]. Wet markets could also transmit zoonotic diseases [32]. The best way to prevent emerging infections is to monitor mutant viruses, herd immunity and vectors for early containment of a potential emerging pathogen.

Development of useful vaccines. As progress of the vaccinology, many useful platforms have been made in genuine vaccine designs that induce effectively protective immunity but less side effects by a recombination with an avirulent vector that encodes a vaccine antigen gene for producing a viral antigen (glycoprotein) responsible for active immunization. Once an emerging infectious pandemic occurs, the vaccine platforms can be applied to make a useful vaccine as shown successful in the development of Ebolavirus vaccines [33,34].

Blockade of virus entry by neutralizing Abs. Both polyclonal and monoclonal antibodies have been shown to rescue fatal emerging infections. Early administration of convalescent plasma containing specific polyclonal antibodies has been shown to significantly reduce the mortality of hospitalized Covid-19 patients [35]. Similarly, convalescent plasma or neutralizing monoclonal antibodies (MoAbs) have also been demonstrated to rescue patients with Ebola, SARS and MERS [36-38] infections. Thus, hyperimmune or recombinant MoAbs of Covid-19 with neutralizing Abs titers administrated as early as possible should be able to decrease virus load and raise better immune response toward balanced Th17/Treg reaction resulting in less severity and also less autoimmunity.

Inhibition of viral replication. Several potential anti-RNA virus agents have been shown to block SARS-CoV-2 entry, replication and/or shedding [39]. The decrease of viral replication and shedding could be made by inhibition of virus-cell fusion, virus and host proteases, lysosome acidification, RNA synthetase and virus budding [39,40]. A proper regimen to combine more than one anti-virus agent may effectively reduce the virus transmission between infected and non-infected cells and raise a better immune response and less mortality [40,41]. A combination of neutralizing MoAbs and anti-virus agent may induce a synergistic effect.

Inhibition of viral shedding. RNA viruses although code 10 more or less structure and nonstructure proteins for replication and evasion of human defense, these viral antigens (glycoproteins) may hijack immunity and/or mediate an enhancement of filopodial protrusion for viral shedding [39]. A recent study in SARS-CoV-2 cell model has shown that inhibition of casein kinase II (CK2) can block viral shedding and suppress inflammatory response [41].

Screening of genetic susceptibility. While a RNA virus invades mucosal epithelium or blood cells, human RNA sensing receptors such as TLR3, RIG-1 (DDX58), TLR7, and/or TLR8, detect the virus and induce interferon production via MyD88, TRIF (TICAM1), IRF3 and/or IRF7 pathways, for suppression of infection by innate immunity [42,43]. While the innate immunity does not eradicate the virus, the viral antigen(s) is(are) presented to T cell-mediated adaptive immunity via recognition of HLA molecules. Different HLA subtypes would cause different disease susceptibility and severity. For instance, the severity of Covid-19 infection has been proposed to be associated with HLA-B*46:01 in a computational simulation by simulating the binding of HLA molecules with Covid-19 whole genome peptides [44]. Deletion or mutation of TLR7 has been also attribute to severity of Covid-19 in young adults [45]. While encountering certain patients who revealed a unique severity different from general patients or a treatment resistance, we need to clarify individual genetic variants and susceptibility.

Regimens to target cytokine storm. Certain RNA viruses do not cause systemic dissemination, but cause systemic immunopathology, resulting in hemorrhage, coaulopathy and/or vascular leakage [46,47]. The emerging infections with immunopathology such as cytokine storm and complement activation of vascular leakage require administration of cytokine antagonist, inhibition of complement cascade or anticoagulant treatment [48-50].

Correcting Th17/Treg imbalance. In response to an RNA virus infection, the host's antigen presenting cells would present the viral antigen to T cells for polarization of naive T helper cells (Tho) toward

a proper Th1 cell immunity and/or Th2 humoral (B cell) response of neutralizing antibody production for viral clearance. Abnormal immune responses with Th17-/Treg imbalance have been shown in some infectious diseases [51,52]. Induction and/or stabilization of Treg cell development is capable to reverse the altered relationship between Th17 and Treg [53]. Microbiota and vitamins have been shown to upregulate Treg functions [54-56]. Treg cells and Vitamin D levels were lower in many Covid-19 patients and associated with an increase in inflammatory cytokines and a risk to severity of pneumonia [56,57]. Moreover, microbiota has been recently shown to coordinate adipocyte-derived mesenchymal stem cells to combat autoimmunity of type 1 diabetes in mice [58], and mesenchymal stem cells (MSC) or their exosomes have been proposed to eliminate hyperinflammation of Covid-19 [59,60]. Appropriate applications of vitamin D, microbiota, MSC and their exosomes may rescue hyperinflammation of an emerging infection with Th17/Treg imbalance (Figure 1).

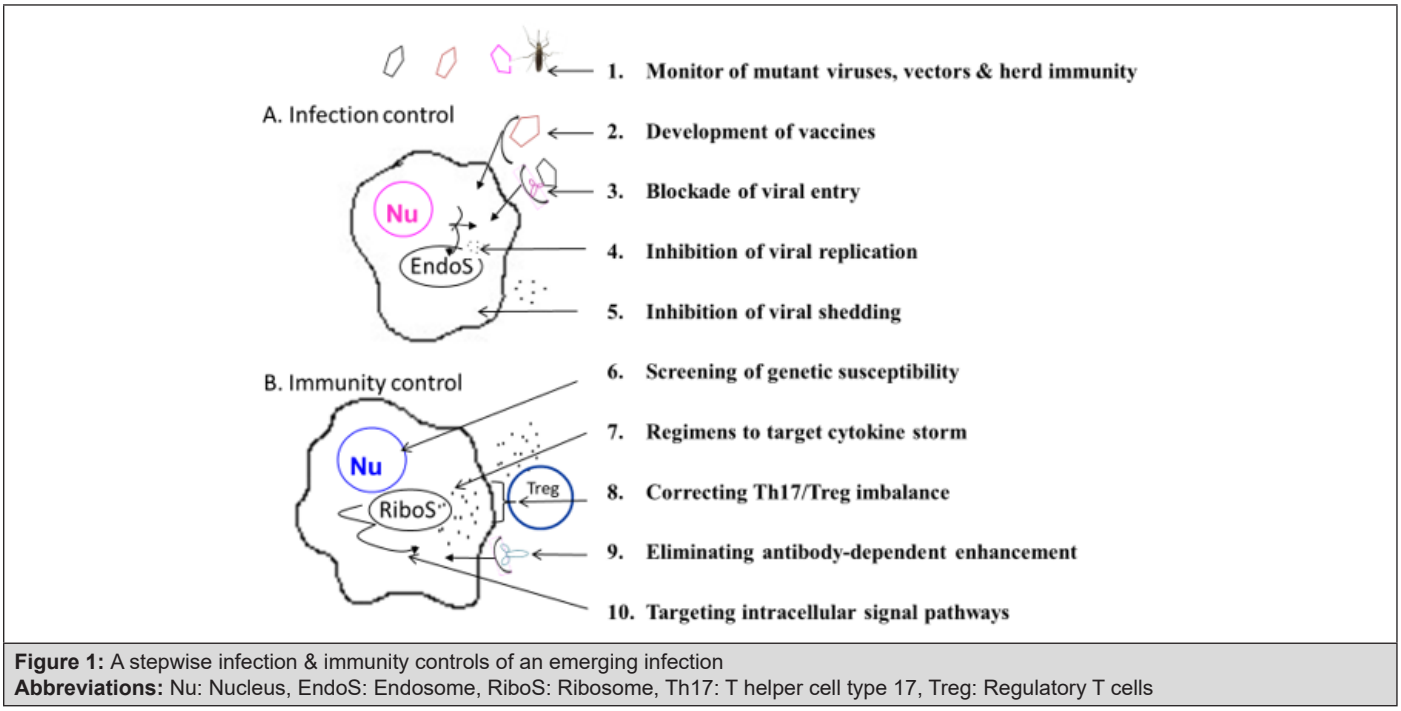

Figure 1: A stepwise infection & immunity controls of an emerging infection
Abbreviations: Nu: Nucleus, EndoS: Endosome, RiboS: Ribosome, Th17: T helper cell type 17, Treg: Regulatory T cells

Eliminating ADE. Antibody-dependent enhancement (ADE) in emerging infections has been concerned in dengue fever and different coronaviruses [61,62]. ADE usually occurs to a sub neutralizing antibody titer or presence of heterotypic antibodies [21,23]. A good way to avoid ADE is to prevent infections or to provide effective immune response. Effective vaccines or neutralizing antibodies are required, but it is not guaranteed whether an effective vaccine could induce another ADE in a subsequent heterotypic infection or the neutralizing antibody titers could decay with time to a sub neutralizing antibody titer for ADE. Another approach to prevent ADE is recently proposed by the elimination of the glycosylation site at N297 of the IgG Fc portion or by a mutation in the Fc region resulting in an effective immune response antibody neutralization but not ADE [61].

Targeting intracellular signal pathways. We and others have shown that certain emerging infections induce hyperactivation of MAPK (e.g. ERK and p38) pathways. Inhibition of p38 activation has been shown to decrease viral replication and cytokine induction in an in vitro cell model. Inhibitors of the phosphokinases which are activated in an in vitro Covid-19 infection, including CK2, CDK, AXL, and PIKFYVE kinases, possess antiviral efficacy. A combination of different inhibitors of the kinases may offer a synergistic effect on anti-virus and anti-inflammatory effects. A recent study showing a combination of viral protease inhibitor, GC376, with the RNA-dependent RNA synthetase inhibitor, remdesivir, causes a sterilizing additive effect. For some infections which could induce infection-associated hemophagocytosis syndrome also called macrophage activation syndrome showing anemia, thrombocytopenia, hyperferritinemia and hypertriglyceridemia may require a combination of IVIG with cyclosporin-A, and/or anti-TNFα [63].

In summary, although each individual emerging infection requires individual strategies to prevent and/or treat the disease morbidity and mortality, the applicable pattern and principle for prevention of an emerging infection may be made in advance for mitigating the pandemic and reducing fatality. A consensus to monitor virus-host-environment interactions in the global village is the most important thing, particularly the potential mutants of emerging RNA viruses and herd immunity of human populations,

poultries, vectors and wild animals. A couple of platforms for developing vaccines with safety and efficacy have been made possible by a recombination of viral antigen gene to an avirulent vector, and a number of models for making monoclonal antibodies have been made capable to neutralize an emerging infection and avoid viral evasion. A combined therapy with different anti-virus agents to inhibit both virus replication and shedding is also feasible. A sequential treatment begins with an anti-viral agent followed by an immunoregulation with neutralizing antibodies or anti-inflammatory regimens may be required for those with potential dissemination or autoimmunity of an emerging infection. In case of certain portion of patients who revealed a treatment resistance, strategies to clarify individual genetic susceptibility and/or pathogenic signal transductions in virus-host-environment interactions are needed for prevention and immunotherapy of a life-threatening emerging infection.

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Conflict of Interest

No Conflict of interest.

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