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Immune response to COVID-19 And herd immunity

A graduation project

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Content

Abstract

As the world is witnessing the pandemic of COVID-19, a disease caused by a novel coronavirus, SARS-CoV-2, emerging genetics and clinical evidences suggest the path of this pandemic. The rapid genomic sequencing and open access data, together with advanced vaccine technology, are expected to give us more knowledge on the pathogen itself, including the host immune response as well as the plan for the herd immunity by vaccination. This research shows a brief picture about the immune system to protect us from COVID-19. It illustrates the process of the immune system, how it works, and mechanism of the immune system to fight virus. At the end, we talk about herd immunity and how can we reach it to protect the world from this virus.

Introduction

The earth is relaxing but human is dying. As of 1st May 2021, more than 3.5 million people died, 171 million have been affected, and at least 200 countries have been affected by corona virus. Most people who are infected with COVID-19 develop an immune response within the first few weeks after infection (1). Research is still ongoing into how strong that protection is and how long it lasts. WHO is also looking into whether the strength and length of immune response depends on the type of infection a person has: without symptoms (‘asymptomatic’), mild or severe. Even people without symptoms seem to develop an immune response (1). At the end of 2019, outbreak of coronavirus that causes respiratory-related illness was reported in Wuhan, Hubei, China, a disease now officially called “the Corona Virus Disease 2019; COVID-19”. The coronavirus that is the causative agent of this respiratory disease was identified and its genome is fully sequenced (2). The genomic sequence of SARS-CoV-2 showed similar, but distinct genome composition of SARS-CoV and MERS-CoV. Since its first reported case in late 2019, the infection has spread to other regions in China and other countries, and the transmission rate, the mortality rate and the clinical manifestation slowly emerged. However, it will take months and maybe years until we will fully grasp the whole picture of the characteristics of the pathogens and its likely origin, symptoms and the host immune responses to combat the infection.

Herd immunity', also known as 'population immunity', is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection (3). WHO supports achieving 'herd immunity' through vaccination, not by allowing a disease to spread through any segment of the population, as this would result in unnecessary cases and deaths. Herd immunity against COVID-19 should be achieved by protecting people through vaccination, not by exposing them to the pathogen that causes the disease. Vaccines train our immune systems to create proteins that fight disease, known as 'antibodies', just as would happen when we are exposed to a disease but – crucially – vaccines work without making us sick. Vaccinated people are protected from getting the disease in question and passing on the pathogen, breaking any chains of transmission (4). Attempts to reach 'herd immunity' through exposing people to a virus are scientifically problematic and unethical. Letting COVID-19 spread through populations, of any age or health status will lead to unnecessary infections, suffering and death. The vast majority of people in most countries remain susceptible to this virus. Most people who are infected with COVID-19 develop an immune response within the first few weeks, but we don't know how strong or lasting that immune response is, or how it differs for different people. There have also been reports of people infected with COVID-19 for a second time. Until we better understand COVID-19 immunity, it will not be possible to know how much of a population is immune and how long that immunity last for, let alone make future predictions. These challenges should preclude any plans that try to increase immunity within a population by allowing people to get infected. Although older people and those with underlying conditions are most at risk of severe disease and death, they are not the only ones at risk (4). We are only beginning to understand the long-term health impacts among people who have had COVID-19, including what is being described as 'Long COVID.' WHO is working with clinicians and patient groups to better understand the long term effects of COVID-19.

Host-Pathogen Interaction

SAR-CoV-2 could be transmitted from human-to-human, via respiratory droplets or close contact (5). A larger study with 425 patients also confirmed human-to-human transmission in which most of the patients (200 out of 277) who were diagnosed during January 1–22, 2020, had never been exposed to either the Wuhan market or been in close contact with individuals with respiratory symptoms. The highly contagious nature of SAR-CoV-2 is probably due to the virus spreading via asymptomatic-infected individual (6).

Immunopathology of COVID-19

The site of initial infection with SARS-CoV-2 is unknown and the pathogenesis of COVID-19 is still under investigation. For most patients, COVID-19 might affect only the lungs because it is mainly a respiratory disease. The primary mode of infection is human-to-human transmission through close contact, which occurs via spraying droplets from infected individual through their cough or sneeze. COVID-19 has a probable asymptomatic incubation period between 2 and 14 days during which the virus can be transmitted (7). At present, the mortality rate of COVID-19 worldwide is approximately 2.4% which are caused by multi-organ failure especially in elderly people and people with underlying health conditions such as hypertension, cardiovascular disease and diabetes (7).

Impacts of Covid-19 on human body

COVID-19 is an RNA virus with a crown like appearance. Its diameter is approximately 60−140 nm. On one side, it has a concave surface with a ridge. It makes a larger binding interface as well as more contacts with ACE2 and have higher affinity, ACE2 is the main receptor for the COVID-19 virus (8). The spike protein present on the surface of COVID-19 gets pinched inside the host cell binding to the ACE2 receptor. Here, the enzyme furin present in the host cell plays a vital role for the virus to enter (9). Then the virus starts to propagate with limited innate immune response and can be detected by nasal swabs. The virus then propagates and reaches the respiratory tract. There it faces a more robust innate immune response. At this stage, the disease is clinically manifest and an innate response cytokine may be predictive of the subsequent clinical course. [The disease will be mild for 80% of the infected patients and mostly restricted to the upper and conducting airways (10). With conservative symptomatic

therapy, these individuals may be monitored and monitored at home. Around 20% of the infected patients will develop pulmonary infiltrates and some of these will develop very severe disease. From Wuhan, 292 COVID-19 patients were studied there. Age was the risk factor of severe patients. When the age of severe patients increased by 5, years, the risk increased by 15.15%. Most of the patients with COVD19 were elderly patients in the severe group with basic diseases. Chronic obstructive pulmonary disease, hypertension, malignant tumor, coronary heart disease, and chronic kidney disease were more frequent in the severe group than in the mild group. From 145 severe cases, 51 patients died, accounting for 34.69% and 90.2% dead patients are over 60 years old. 40 patients had basic disease out of 51 deaths, accounting for 78.43%. Recent reports show that patients with more than 60 years of age and having comorbidities, especially hypertension are believed to be risk factors for severe disease and death from SARS-CoV-2 infection (11).

Mechanism of immune systems in human body against COVID-19

The immunity system supports our body's natural ability to defend against pathogens and resist infections. As long as the immune system runs smoothly, we do not notice infections like COVID-19. Our immune system can be categorized into three categories. They are, namely, innate immunity (rapid response), adaptive immunity (slow response), and passive immunity. Passive immunity is again two types and they are natural immunity which we receive from our mother and artificial immunity that we receive from medicine. However, when our body encounters any germs or viruses for the first time, the immune system cannot work properly and we become sick. The same thing has happened in the case of COVID-19 (12). After being affected by virus, immune responses to mediate antibody occur. The B cells are assisted by T cells to differentiate into plasma cells, which in return produce antibodies specific to a viral antigen. Neutralizing nature antibody is efficient in fully blocking the virus from entering into host cells to limit the infection and plays a very intense protective role at the later stage of infection and prevents relapse of infection in the future. In contrast, a cellular immunity response can be seen inside the

infected cells, which is mediated by T-lymphocytes. The overall adaptive immune response is directed by helper T cells, while cytotoxic T cells play a vital role in the clearance and cleaning of viral infected cells (13).

Innate Immune Responses to COVID-19

Currently, only limited information is available on the host innate immune status of SARS-CoV-2 infected patients. In one report where 99 cases in Wuhan were investigated, increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum IL-6 (52%) and increased c-reactive protein (84%) were observed. Increased neutrophils and decreased lymphocytes also correlate with disease severity and death (14). Furthermore, patients needing ICU care had higher plasma levels of many innate cytokines. These clinical features suggested the likelihood of involvement of highly pro-inflammatory condition in the disease progression and severity (14). One study, according to pro-inflammatory cytokines compare between severe and mild cases under investigation, it suggests that IL-1 could play a unique role in driving pathogenesis (15). And also demonstrated that pro-inflammatory cytokines were not elevated in mild COVID-19 (15). That indicate that a heightened pro-inflammatory response is characteristic of severe COVID-19.

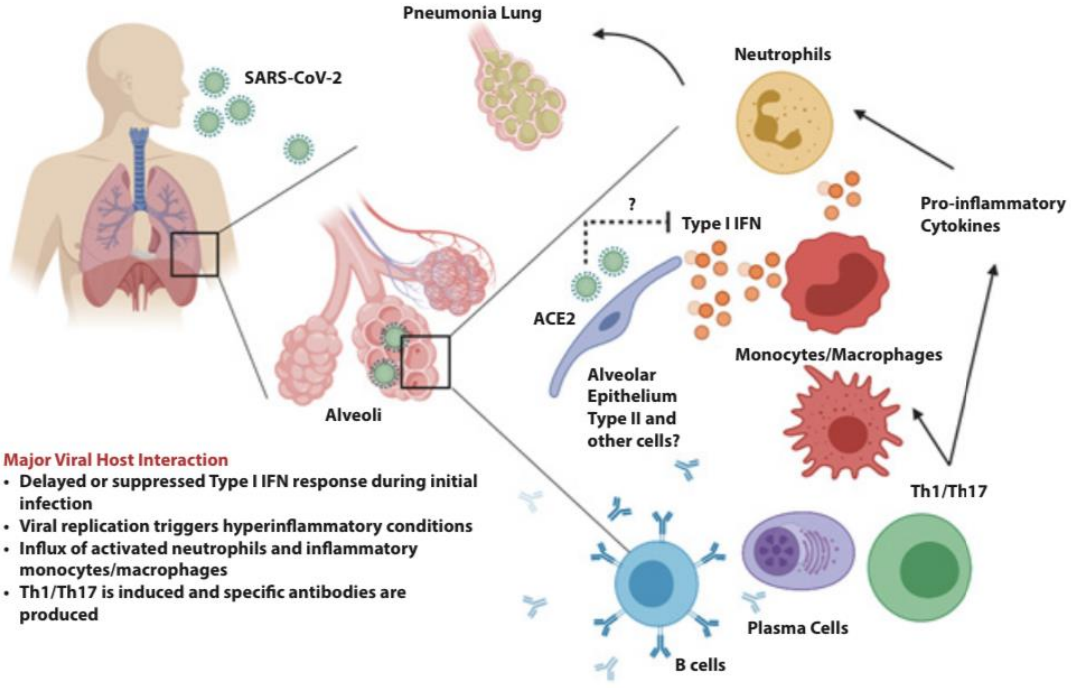

Figure1. Proposed host immune responses during SARS-CoV-2 infection Aerosolized uptake of SARS-CoV-2 leads to infection of ACE2 expressing target cells such as alveolar type 2 cells or other unknown target cells. Virus may dampen anti-viral IFN responses resulting in uncontrolled viral replication (16). The influx of neutrophils and monocytes/macrophages results in hyper-production of pro-inflammatory cytokines. The immunopathology of lung may be the result of the "cytokine storms". Specific Th1/Th17 may be activated and contributes to exacerbate inflammatory responses (16). B cells/plasma cells produce SARS-CoV-2 specific antibodies that may help neutralize viruses (16). The question marks indicated events that are still speculative or unknown.

Adaptive Immune Responses to COVID-19

The adaptive immune system plays a pivotal role in SARS-CoV-2 clearance via activated cytotoxic T-cells that destroy infected cells and through B-cells that produce neutralizing antibodies against virus-specific anti gens (Figure 2). A key feature of COVID-19 is blood lymphopaenia, with reduced numbers of CD4+ T-cells, CD8+ T-cells, and B-cells. Lymphopaenia may be partially explained by an abnormal innate immune response featuring low IFN-I, considering its essential role in the assembly of viral material for antigen presentation and the subsequent induction of adaptive immunity (18). Other mechanisms that potentially contribute to COVID-19-associated lymphopaenia include direct SARS-CoV-2 infection of T-cells, cytokine induced apoptosis and pyroptosis of lymphocytes, MAS-related haemophagocytosis, lymphocyte sequestration in the lungs or other organs, reduced bone marrow hematopoiesis, and virus-induced tissue damage of lymphatic organs (19).

, the vast majority of COVID-19 patients with mild-to-moderate disease experience a robust adaptive immune response consisting of T-cells (against S-protein- and nucleoprotein/membrane protein-derived antigens) and neutralizing antibodies (against S-protein-derived antigens), which persists for months after primary infection (20,21).

Overall, coordinated SARS-CoV-2-specific adaptive immune responses are associated with milder disease and are therefore essential for optimally controlling viral infection (22).

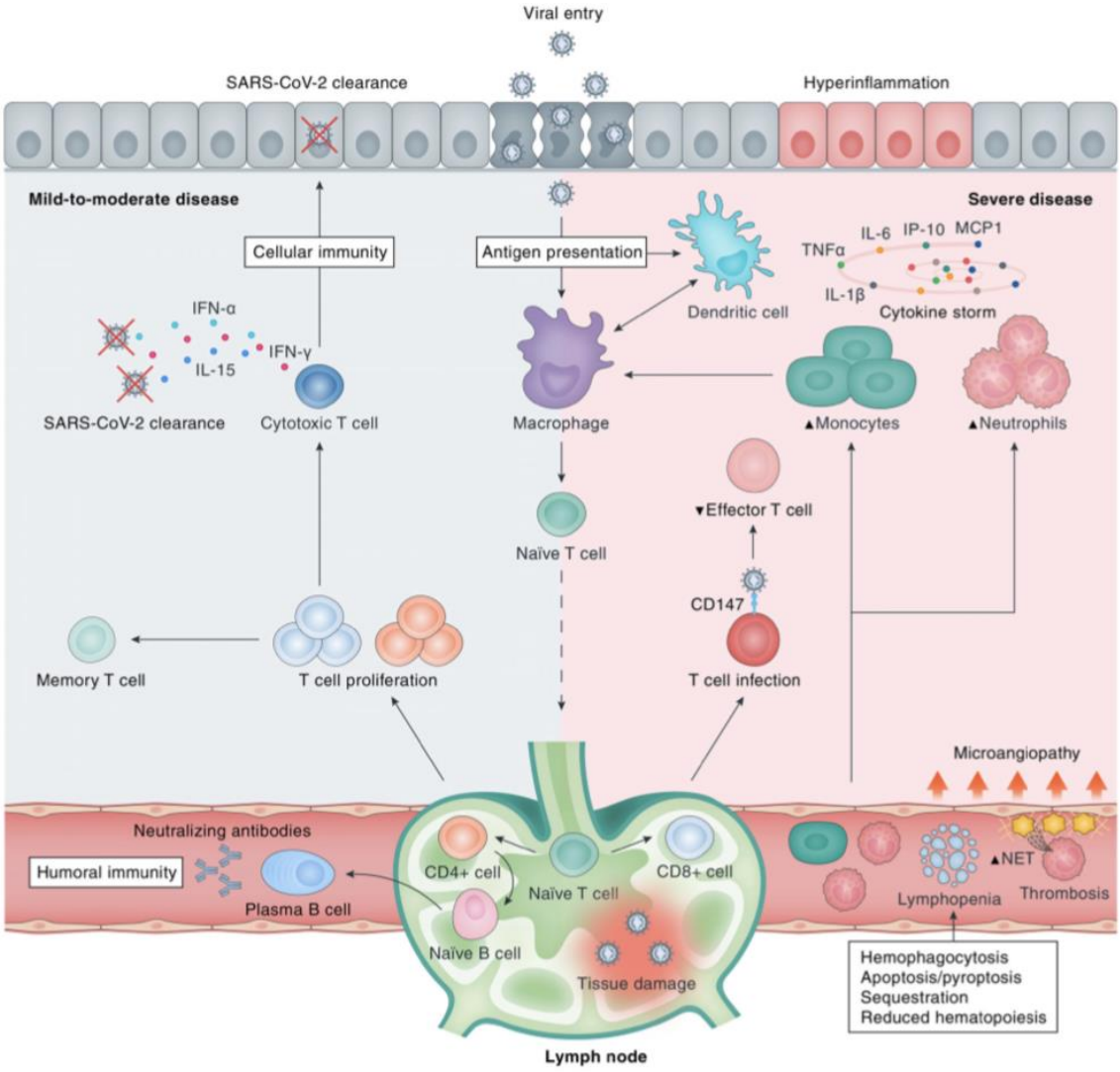

Figure 2. Immunological response to SARS-CoV-2 infection.

Upon viral cell entry, SARS-CoV-2 antigens are processed by the innate immune system through antigen-presenting cells (APCs), e.g. epithelial cells, macrophages, and/or dendritic cells. Subsequently, the adaptive immune system is activated by migration of APCs to the lymphoid system (23). Upon antigen recognition, T-lymphocytes proliferate and differentiate into CD4+ and CD8+ T-lymphocytes that are responsible for sequential events including cytokine production, activation of naïve B-lymphocytes, and clearance of infected cells (CD8+ cytotoxic T-lymphocytes) (24). B-lymphocytes proliferate and differentiate into plasma cells that produce large numbers of neutralising antibodies, representing humoral immunity. A bulk of cytokines is induced upon SARS-CoV-2 infection, most of which contribute to hyperinflammation as constituents of the 'cytokine storm' in severe disease (e.g. IL-6, TNF-α, IL-1β, IP-10, MCP-1, CSFs, and IL-17A), whereas others are particularly important for viral clearance (e.g. IL-15, IFN-α, IL-12, IL-21, and IFN-γ) in mild-to moderate disease.

Severe COVID-19 is marked by dysfunction of certain immune cells, with relatively increased abundances of neutrophils and monocytes and decreased levels of effector T-lymphocytes (25). In addition, multiple downstream pathophysiological processes are activated, including an increased thrombogenic state [microangiopathy, formation of neutrophil extracellular traps (NETs)], haemophagocytosis, reduced haematopoiesis, and increased apoptosis/pyroptosis (26).

Individual variation and COVID-19

Further important information on immune mechanisms capable of controlling COVID-19 may come from females and pediatric patients. Indeed, in most instances, children develop a mild form of the disease. Different explanations could be proposed. Thus, children, in view of the high plasticity of their adaptive responses, particularly in their B-cell compartment, could more efficiently clear the virus (27). To this favorable situation may contribute also innate immunity, challenged/trained by frequent infections and by vaccines/adjuvants administered in early life. In addition, the lower susceptibility of children to SARS-CoV-2 could be due to the lower density of angiotensin-converting enzyme 2 (ACE2) receptors as compared with adults (28). The lower frequency of infection and mortality in women could be related to hormonal and genetic differences, to lower incidence of comorbidities affecting the lung (chronic obstructive pulmonary disease, smoke, etc.), or to higher prevalence of autoimmune and allergic disorders, as the result of some decreased regulatory mechanism (28). In comparison with men, women usually show:

(1) less viral load levels and less inflammation with higher CD4+ T cells and antibody responses.
(2) lower expression of ACE2 in the lung.
(3) overexpressed TLR8, CD40L, and CXCR3 (encoded by X chromosome), all influencing antiviral response; and
(4) overexpressed TLR7 (the crucial sensor for RNA viruses such as SARS-CoV2), which, when triggered by the virus, leads to higher IFN-1 and lower IL-6 production (29).

Differences in immune response in asymptomatic versus severe COVID-19 cases Infection

In a new study to understand how different immune cells responded to the infection, a large team of researchers came together to analyze blood from 130 people with COVID19. These patients came from three different UK centers (Newcastle, Cambridge and London) and ranged from asymptomatic to critically severe. The team performed single cell sequencing from ~800,000 individual immune cells, along with detailed analysis of cell surface proteins and antigen receptors found on immune cells in the blood. They revealed differences in multiple types of immune cells that are involved in the body's response to COVID19. In those with no symptoms, the team found increased levels of B cells that produce antibodies that are found in mucus passages, such as the nose. These antibodies may be one of our first line of defense in COVID19. However, these protective B cells were missing in people with serious symptoms, indicating the importance of an effective antibody associated immune response at the nose and other mucus passages. The team discovered that whereas patients with mild to moderate symptoms, had high levels of B cells and helper T cells, which help fight infection, those with serious symptoms had lost many of these immune cells, suggesting that this part of the immune system had failed in people with severe disease. In contrast, people with more serious symptoms leading to hospitalization had an uncontrolled increase in monocytes and killer T cells, high levels of which can lead to lung inflammation. Those with severe disease also had raised levels of platelet producing cells, which help blood to clot (30).

Basic Concepts of Herd Immunity

Acquired immunity is established at the level of the individual, either through natural infection with a pathogen or through immunization with a vaccine. Herd immunity (the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population) stems from the effects of individual immunity scaled to the level of the population (31). This population-level effect is often considered in the context of vaccination programs, which aim to establish herd immunity so that those who cannot be vaccinated, including the very young and

immunocompromised, are still protected against disease (32). Depending on the prevalence of existing immunity to a pathogen in a population, the introduction of an infected individual will lead to different outcomes (Figure 3). In a completely naive population, a pathogen will propagate through susceptible hosts in an unchecked manner following effective exposure of susceptible hosts to infected individuals. However, if a fraction of the population has immunity to that same pathogen, the likelihood of an effective contact between infected and susceptible hosts is reduced, since many hosts are immune and, therefore, cannot transmit the pathogen. If the fraction of susceptible individuals in a population is too few, then the pathogen cannot successfully spread, and its prevalence will decline. The point at which the proportion of susceptible individuals falls below the threshold needed for transmission is known as the herd immunity threshold (33). Above this level of immunity, herd immunity begins to take effect, and susceptible individuals benefit from indirect protection from infection (Figure 3B). Under the simplest model, the herd immunity threshold depends on a single parameter known as R0, or the basic reproduction number (Figure 2A). R0 refers to the average number of secondary infections caused by a single infectious individual introduced into a completely susceptible population (33). If we consider a hypothetical pathogen with an R0 of 4, this means that, on average, one infected host will infect four others during the infectious period, assuming no immunity exists in the population. Therefore, the more communicable a pathogen, the greater it's associated R0 and the greater the proportion of the population that must be immune to block sustained transmission (Figure 2B). A similar parameter important for understanding population-level immunity is the effective reproduction number (Re or Rt). Re is defined as the average number of secondary cases generated by a single index case over an infectious period in a partially immune population (34). Unlike R0, Re does not assume a completely susceptible population and, consequently, will vary depending on a population's current immune state, which will change dynamically as an outbreak event or vaccination campaign unfolds. Ultimately, the goal of vaccination programs is to bring the value of Re below 1. This occurs when the proportion of the population with immunity exceeds the herd immunity threshold. At this point, pathogen spread cannot be maintained, so there is a decline in the number of infected individuals within the population (35).

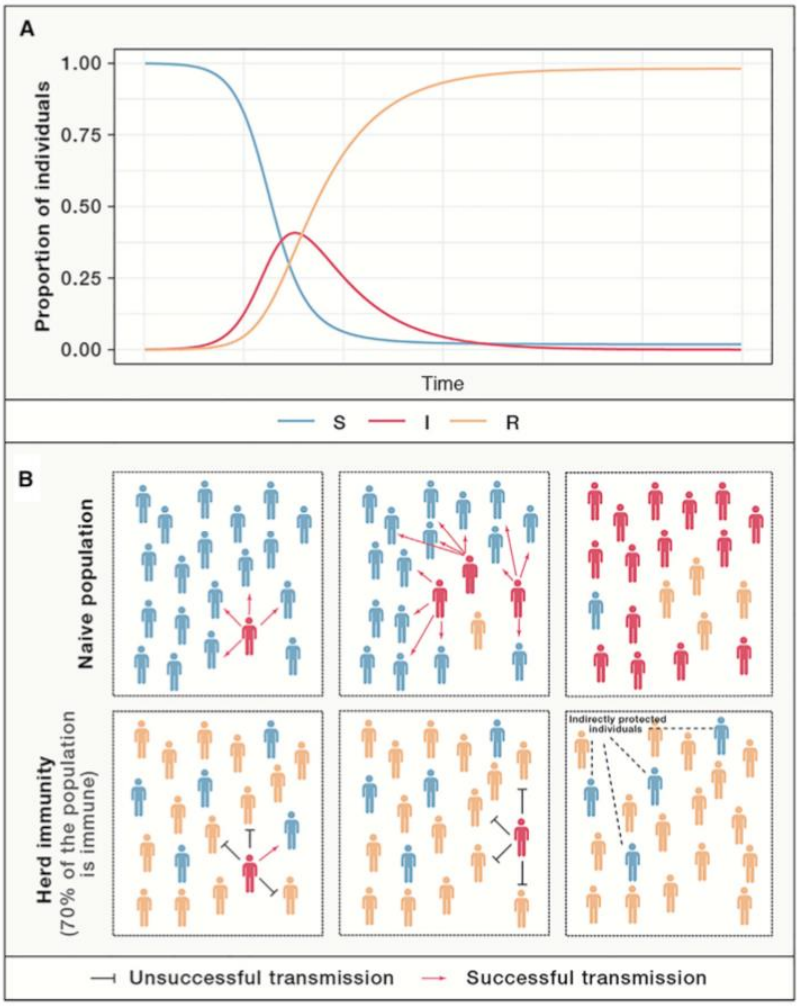

Figure 3. Herd Immunity

(A) SIR (susceptible, infectious, recovered) model for a completely immunizing infection with an R0 = 4. The model assumes a closed population in which no people leave and no new cases are introduced. Following the introduction of a single infected individual, the proportion of infected individuals (red line) increases rapidly until reaching its peak, which corresponds to the herd immunity threshold. After this point, newly infected individuals infect fewer than one susceptible individual, as a sufficient proportion of the population has become resistant, preventing further spread of the pathogen (orange line) (35).

(B) Schematic depiction of the disease propagation dynamics when one infected individual is introduced into a completely susceptible population (top panel) versus a situation in which an infected individual is introduced into a population that has reached the herd immunity threshold (bottom panel). In the naive population, an outbreak quickly emerges, whereas under the scenario of herd immunity, the virus fails to spread and persist in the population(35).

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