Thinking About Waning Immunity

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Global measles vaccination coverage across first and second dosages has reached a global maximum of approximately 83% as of 2024 (World Health Organization, 2026). At such a high level, it is natural to assume herd immunity and that measles infection should be largely impossible, yet outbreaks continue to occur across Canada and the United States, which are two notably developed countries (Centers for Disease Control and Prevention, 2026; BlogTO, 2026). This apparent contradiction highlights the importance of understanding how immunity changes over time, as such, examining waning immunity at both the individual and population levels through in-host models (immuno-epidemiology) reveals how the immune memory dynamics of the individual and the specific virus pathogenesis shape disease transmission and long-term epidemic behavior, offering biological and mathematically supported insights that can help guide vaccination strategies and improve public health responses to infectious disease outbreaks.

The measles virus provides a particularly clear example of how immunological mechanisms shape epidemiological outcomes. Measles is a single-stranded RNA virus transmitted through respiratory droplets. After entering through the respiratory tract, viral replication initially occurs in the respiratory tract's lymphocytes, dendritic cells, and alveolar macrophages. These peripheral blood mononuclear cells (PBMCs) provide a mechanism for systemic dissemination, allowing the virus to spread to lymphoid tissues and later to the skin and other organs. The measles rash corresponds to the immune response rather than the direct cytopathic effects of the virus itself, appearing in roughly 10–14 days after infection, with peak viral load occurring around the same time (Kondamudi, Tobin, & Waymack, 2026).

From an immunological perspective, viral clearance in measles infection emerges from the coordinated interaction between the innate and adaptive immune systems. The innate immune system provides the first line of defense immediately after infection and helps limit early viral replication, but it is generally insufficient to completely eliminate the virus. Instead, the adaptive immune response ultimately determines the outcome of infection. The adaptive immune system consists of two complementary branches: humoral immunity and cell-mediated immunity. Humoral immunity is mediated by antibodies produced by B lymphocytes, which bind viral antigens and help neutralize viral particles before they infect new cells. However, while antibodies are important in preventing infection or reinfection, their role in clearing measles virus once infection has been established appears limited (Janeway, Travers, Walport, & Shlomchik, 2001). Empirical evidence suggests that antibody presence alone does not necessarily eliminate the virus during active infection (Heffernan & Keeling, 2008).

Instead, cell-mediated immunity, specifically, cytotoxic CD8 T-lymphocytes, play the dominant role in clearing infected cells. Once activated, CD8 T-cells destroy infected cells through cytolytic mechanisms, thereby halting viral replication. In the in-host model developed by Heffernan and

Keeling, this process is represented mathematically through interaction terms between infected cells and activated CD8 T-cells, where activated immune cells remove infected cells from the system (Heffernan & Keeling, 2008). This immune-mediated killing is one of the key mechanisms driving the rapid decline in viral load observed after peak infection. These cells recognize viral antigens presented on infected cells and induce apoptosis, effectively removing viral replication sites (Janeway et al., 2001).

In the mathematical framework of the model, this transition from activated to memory cells is explicitly represented, allowing the model to track how immune memory develops and decays over time (Heffernan & Keeling, 2008). The model explicitly tracks six biological quantities: uninfected PBMCs (x), infected cells (y), free virus particles (v), naïve CD8 T-cells (w), activated CD8 T-cells (z), and memory CD8 T-cells (m). These variables are connected through a system of nonlinear ordinary differential equations that represent the biological processes governing infection, immune activation, and immune memory formation.

$$\frac{dx}{dt} = \lambda_x - d_x x - \beta q x v, \tag{1}$$

$$\frac{dy}{dt} = \beta q x v - d_y y - \xi y z, \tag{2}$$

$$\frac{dv}{dt} = k y - u v - \beta q v x, \tag{3}$$

$$\frac{dw}{dt} = \lambda_z - \frac{cqvw}{C_1 q v + K_1} - d_w w, \tag{4}$$

$$\frac{dz}{dt} = \frac{cqvw}{C_1 q v + K_1} + \frac{pqvz}{C_2 q v + K_2} - (\rho + d_z) z + \frac{f c_m q v m}{C_3 q v + K_3}, \tag{5}$$

$$\frac{dm}{dt} = \rho z - d_m m - \frac{c_m q v m}{C_3 q v + K_3}. \tag{6}$$

The first three equations describe viral replication and infection dynamics. Uninfected immune cells are produced by the bone marrow at rate λ_x and are removed either through natural death or infection by viral particles. Infection occurs through a mass-action interaction between susceptible cells and infectious virions, represented by the term $\beta q x v$, where q denotes the fraction of virions that are infectious. Infected cells then produce new virions at rate k. while virions themselves are cleared from the system at rate u. Activated CD8 T-cells eliminate infected cells through cytotoxic activity, represented by the interaction term $\xi y z$. Together, these processes generate the characteristic trajectory of measles infection: viral replication rises rapidly during early infection, reaches a peak around the onset of symptoms, and then declines quickly as the immune response intensifies.

The remaining equations describe the immune response. Activated CD8 T-cells then proliferate and participate in the destruction of infected cells, while a portion of these cells eventually differentiate into memory T-cells at rate r, which can respond more rapidly upon subsequent exposure to the pathogen because they no longer require the same activation process as naïve cells. This immune memory forms the basis of both natural immunity following infection and immunity induced by the live attenuated measles vaccine. However, immune memory can gradually decline in the absence of antigen exposure, a process referred to as waning immunity, represented through the memory CD8 T-cell decay parameter d_m. The initial level of immune memory m_0 strongly influences the trajectory of infection (at the within-host level). This is an important modeling choice

because it translates the biological idea of fading immune memory into a measurable mathematical mechanism, which then becomes the basis for later epidemiological analysis (Heffernan & Keeling, 2008).

An analytical result that emerges from the model is the derivation of the within-host basic reproductive ratio R_0, which measures the expected number of newly infected cells produced by a single infected cell in a completely susceptible host environment (Heffernan & Keeling, 2008). This threshold behavior mirrors the concept of the basic reproductive number in epidemiology, illustrating how similar mathematical principles govern infection dynamics across both cellular and population scales.

$$R_0 = \frac{k}{d_y} \frac{\beta q x_0}{\beta q x_0 + u}$$

Using these infected-cell dynamics, Heffernan and Keeling estimate thresholds for infectiousness and symptomatic disease as a function of pre-existing memory CD8 T-cell levels. Individuals with lower initial immunity will transmit measles symptomatically, while individuals with higher levels of memory will still transmit asymptomatically. They also show that post-exposure immune boosting is non-monotonic: the boosted level of memory first decreases and then increases as initial memory rises. This is conceptually important because it implies that immunity is not simply "high" or "low," but behaves dynamically in a way that changes both individual disease severity and population transmission patterns (Heffernan & Keeling, 2008). Some basic examples could be that individuals with low immune memory experience ($m_0 = 0$) large infections and symptomatic transmission, whereas individuals with intermediate levels of immune memory may transmit the virus asymptomatically (less effective transmission) and experience milder symptoms.

The model also allows the authors to investigate the immunological effects of vaccination. The attenuated (weakened) virus in the vaccine replicates less efficiently but still produces a sufficient immune stimulus to activate naïve CD8 T-cells and generate immune memory. The resulting infection dynamics differ substantially from natural infection: the infected PBMC population remains very small, viral load rises only modestly, and the immune response clears the virus rapidly. In the simulations, the peak memory CD8 T-cell population following vaccination is at a lower level produced during natural infection, but, this reduced immune memory is nevertheless sufficient to provide long-term protection, because the level is comparable to the immunity observed approximately four years after natural infection. This shows that vaccinated individuals retain substantial protection against symptomatic disease and transmission for extended periods of time (Heffernan & Keeling, 2008).

When a second vaccine dose is introduced several years after the first through a booster administered at age five, the immune system responds more rapidly due to the presence of pre-existing memory CD8 T-cells. This results in a stronger secondary immune response and an increase in the overall memory CD8 T-cell population. In the model simulations, the booster dose elevates immune memory to levels slightly higher than those achieved following the initial vaccination (Heffernan & Keeling, 2008).

After demonstrating that the in-host model reproduces the immunological dynamics of measles infection and vaccination, Heffernan and Keeling extend this framework to investigate how these within-host mechanisms influence population-level disease dynamics (Heffernan & Keeling, 2009). The motivation for this extension arises from a limitation of population-level compartmental epidemiological models. Standard compartmental models (SEIR-V) typically assume that immunity following infection or vaccination is permanent and that individuals can be categorized simply as

susceptible, infectious, or recovered. However, the in-host model developed in the first study suggests that immunity behaves as a continuous and dynamic quantity governed by immune memory, as the level of memory CD8 T-cells present at the time of exposure determines whether infection becomes symptomatic, asymptomatic, or suppressed entirely, and it also influences the probability of transmission and the degree of immune boosting that occurs following exposure. These results imply that individuals within a population may possess widely varying levels of immunity, and that this variation can significantly alter the transmission potential of the pathogen. As a result, the authors incorporate waning immunity and immune boosting into an epidemiological framework in order to examine how the distribution of immune memory within a population shapes long-term measles dynamics and vaccination outcomes (Heffernan & Keeling, 2009).

To move from the within-host scale to the population scale, Heffernan and Keeling modify the standard SEIR framework to include the level of CD8 T-cell memory (Heffernan & Keeling, 2009). They stratify the susceptible, exposed, infectious, and recovered classes by an immune-memory index $i \in N$, which represents the level of CD8 T-cell memory carried by an individual. These states evolve over time as immunity wanes during disease-free periods and is boosted again upon re-exposure. Mathematically, this means that each immune class i has its own susceptible, exposed, infectious, and recovered compartments, denoted S_i, E_i, I_i, R_i. Individuals move between these classes according to both infection dynamics and immune-memory dynamics. The terms involving w_i describe waning immunity, pushing individuals from higher immune-memory classes to lower ones over time. By contrast, the boosting terms $b_{i,j}$ describe movement upward in immune status after exposure or infection, so that an encounter with measles can restore immune memory even if it does not result in severe symptomatic disease.

$$\frac{dS_0}{dt} = B + qR_0 + w_1 S_1 - \lambda S_0 - dS_0, \tag{7}$$

$$\frac{dS_i}{dt} = qR_i + w_{i+1} S_{i+1} - \lambda S_i - dS_i - w_i S_i, \tag{8}$$

$$\frac{dE_i}{dt} = \lambda S_i - a_i E_i - dE_i, \tag{9}$$

$$\frac{dI_i}{dt} = a_i E_i - g_i I_i - dI_i, \tag{10}$$

$$\frac{dR_i}{dt} = w_{i+1} R_{i+1} + \sum_j b_{i,j} g_j I_j - w_i R_i - qR_i, \tag{11}$$

$$\lambda = \sum_i b_i I_i. \tag{12}$$

Within this framework, immune boosting becomes a central mechanism. Individuals with low immune memory may develop full symptomatic infection, while individuals with moderate immunity may experience asymptomatic or subclinical infection that still boosts their immune memory. Those with sufficiently high immune memory may clear the virus so quickly that they do not meaningfully transmit at all, but their exposure can still refresh their immunity (Heffernan & Keeling, 2009).

However, most noticeably, in the model, individuals gradually move from higher immune-memory classes to lower ones due to waning immunity when they are not re-exposed to the pathogen. Over time, this process causes the distribution of immune memory in the population to shift downward, meaning that a growing fraction of individuals occupy intermediate immune states rather

than the highest levels of protection. For example, individuals who are infected but asymptomatic do not get detected and can contribute to hidden transmission chains within the population, individuals whose immunity has waned sufficiently may reenter states where symptomatic infection becomes possible and the number of these partially susceptible individuals increases, and the population becomes capable of supporting renewed outbreaks. This would explain why measles outbreaks seem perpetual, but of course understandable, due to the large human contact networks everyone uncontrollably has. In the simulations presented in the paper, the system may experience extended periods with very low case numbers followed by sudden large outbreaks. These outbreaks occur when enough individuals have transitioned into lower immune-memory classes to allow sustained transmission. Because the accumulation of susceptible or partially susceptible individuals occurs gradually, the resulting epidemic waves can appear irregular and may be separated by long disease-free intervals (Heffernan & Keeling, 2009).

In both the in-host model and the epidemiological model, vaccination against measles substantially lowers viral replication and transmission as people are exposed much less often. Pathogens can traverse large populations through surprisingly short chains of interactions. The population-level model shows that immunity in the population becomes dynamic as immune memory naturally declines, which may require things like booster doses, continued surveillance and high vaccination coverage. Modern public health relies on vaccination programs and boosters, beyond natural infection and repeated exposure. Vaccination provides a mechanism to sustain immunity while preventing the large epidemic waves that would otherwise arise in highly connected populations.

On a personal note, tangentially related to immuno-epidemiology: I was reminded that a couple of months ago, my close friend encouraged me to submit a public comment to the CDC's Advisory Committee on Immunization Practices (as we are both American) regarding potential changes to the hepatitis B birth-dose recommendation, to help bridge the gap between scientific evidence and public perception of vaccines. In the case of hepatitis B, early vaccination not only prevents infection but also dramatically reduces the risk of chronic disease and liver cancer later in life and delaying or removing the automatic birth dose eliminates a key layer of protection because real-world uptake drops substantially when hospital administration is no longer the default. Obviously the universal birth dose should not be delayed, but perhaps many people do not realize that vaccination policies should hinge on the insights discovered through infectious disease models including in-host modeling, and that vaccination policies are in needed to prevent long-term health consequences for everyone by reducing the probability of individuals entering high-risk infectious states. It became clear to me that mathematical models of immunity and transmission are not purely theoretical; they also must continue to play the primary role in real-world public health decisions. Ultimately that experience further motivated my interest to study epidemiology.

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