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Insights into Cytomegalovirus Transmission Dynamics: Bridging the Gap between Mathematical Modeling and Public Health Strategies

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Abstract

This mini-review delves into the crucial role of mathematical modeling in understanding cytomegalovirus (CMV) transmission dynamics. While infectious disease modeling often focuses on the population level, it is essential to recognize that immune development takes place at the individual level. This review explores recent advancements in both stochastic and deterministic modeling approaches and their contributions to our understanding of CMV transmission. Stochastic modeling enables us to investigate the efficiency and risk factors associated with CMV transmission in high- risk populations, such as hematopoietic stem cell transplantation (HCT) recipients, shedding light on factors influencing transmission. Deterministic modeling emphasizes the importance of viral replication, immune response, transmission efficiency, and the role of vectors. It underlines the need for a comprehensive understanding of these factors to develop effective prevention and control strategies. Integrated deterministic and stochastic models offer a holistic perspective, explaining phenomena like prolonged oral CMV shedding during primary infection and highlighting the importance of timing and immune suppression levels in transplacental transmission risk. In conclusion, these modeling insights can be integrated into public health strategies for CMV management, including targeted pre- transplant screening, enhanced post-transplant surveillance, optimized immune-based interventions, minimized transmission risks in HCT, vector control, and timing-sensitive intervention guidelines. This comprehensive approach can substantially enhance CMV prevention and control efforts, benefiting vulnerable populations and the broader community.

Keywords: Cytomegalovirus; Stochastic Model; Deterministic Model; Public Health

Abbreviations: HCT: Hematopoietic Stem Cell Transplantation; HIG: Hyperimmune Globulin; CDC: Centers for Disease Control; CMV: Cytomegalovirus.

Introduction

Cytomegalovirus is a major public health concern due to its wide prevalence and potential for severe complications, especially in vulnerable populations. Mathematical modeling has proven invaluable in dissecting the dynamics of CMV transmission. Most mathematical modeling of infectious diseases primarily focuses on the population level. Throughout the COVID-19 pandemic, numerous studies have adopted this approach [1-14]. While these studies address critical aspects like vaccine efficacy and waning immunity at a broader scale, it's essential to recognize that the actual

development of immunity occurs within an individual. Within host mathematical modeling delves into the dynamics of pathogen reproduction and cellular infection within a single person. This approach has proven effective in understanding various diseases. This mini-review paper explores recent advancements in both stochastic and deterministic modeling approaches and their contributions to our understanding of CMV transmission. The paper is structured as follows: Section 2 explores stochastic approaches and the insights they offer, followed by Section 3, which delves into deterministic approaches. In Section 4, we introduce papers that merge both deterministic and stochastic methods to gain a more comprehensive understanding. Finally, in Section 5, we outline public health strategies that aim to address the insights derived from these mathematical models.

Stochastic Modeling

Stochastic modeling is a valuable tool for understanding the transmission dynamics of infectious diseases. It allows for the incorporation of randomness and uncertainty into the models, which can better capture the inherent variability in disease transmission. Stochastic models have been used to study a wide range of infectious diseases, including influenza [15], COVID-19 [16], chickenpox [17], and respiratory syncytial virus (RSV) [18].

In the context of CMV transmission, stochastic modeling has been used to investigate the efficiency and risk factors associated with CMV transmission in hematopoietic stem cell transplantation (HCT) recipients [19]. Authors found that CMV infection dynamics in untreated HCT recipients vary widely among individuals, with slow viral clearance suggesting a compromised immune response post-transplant. Ultimately, the study suggests that the host's immune response plays a crucial role in controlling CMV infection in this population, emphasizing its significance for potential treatment and prevention strategies.

Stochastic modeling can be used to explore the relationship between primary infection conditions, latent viral burden, and the risk of recurrence, providing insights into the stochastic events of recurrence in different organs. In Reddehase MJ, et al. [20], authors examined the conditions of primary CMV infection and their impact on the risk of recurrent CMV disease. They found that the copy number of latent viral genomes in tissues is a key parameter that determines the overall and organ-specific risks of recurrence Reddehase MJ [20].

Deterministic Modeling

Deterministic modeling of CMV transmission involves the use of mathematical models to understand the spread and dynamics of the virus. These models can provide insights into the factors that influence transmission and inform strategies for prevention and control.

One important aspect of CMV transmission is the role of viral replication and spread. A study by Kepler GM [21] presents a mathematical model of human CMV infection, emphasizing its significance in immunosuppressed transplant patients. It delineates four stages of human CMV infection and develops a mechanistic mathematical model using ordinary differential equations to describe infection dynamics at the cellular and viral levels. The model is validated to accurately represent primary and latent human CMV infections in immunocompetent individuals and demonstrates secondary (reactivated) infections in immunosuppressed patients, particularly relevant to transplant scenarios.

In Michael Gabel [22], authors investigate the dynamics of CMV-specific CD8+ T cell responses within individual hosts, focusing on the phenomenon of "memory inflation". Memory inflation refers to the sustained expansion of CMV-specific CD8+ T cells in response to certain CMV-derived peptides and has implications for T cell-based vaccine development against various diseases. The research combines experimental data and mathematical models to analyze the dynamics of these CD8+ T cells in mice infected with MCMV. The study reveals that mathematical models assuming different viral stimuli during acute infection and the memory inflation phase provide a more accurate description of observed dynamics than models assuming similar viral stimuli in both phases. Additionally, the study quantifies the different phases of memory inflation in individual mice, highlighting consistency in timing but significant variation in response size among mice.

Integrated Deterministic and Stochastic Models for Understanding Cmv Transmission

While stochastic models have been employed in various studies of infectious disease spread at the population level, when considering risk factors associated with CMV, the modeling framework can become quite complex in certain scenarios. This complexity often necessitates numerous Monte Carlo simulations to accurately capture the uncertain epidemic trajectories [23]. Conversely, the deterministic model offers more computationally efficient option and approximates its corresponding stochastic model at the population mean level as the sample size increases, in accordance with the law of large numbers. This implies that as the population grows, the probability of specific infections converges, primarily influenced by the initial conditions and input parameter values [24].

There has been work that aims to model CMV transmission by integrating deterministic and stochastic models. In one study Mayer BT [25], authors examined a cohort of Ugandan infants who were followed prospectively from birth. These infants are at risk of primary CMV infection through various routes, including oral transmission. They used deterministic mathematical modeling to demonstrate that prolonged oral CMV shedding during primary infection can be explained by slow viral expansion and inefficient immunologic control. Then in a later study Mayer BT [26], authors investigated a cohort of highly exposed CMV-uninfected infants in Uganda. Authors incorporated parameters derived from the aforementioned previous study [25]. These parameters, including viral replication spread and decay rates, and the rate of infected-cell death, which would have been challenging to acquire without the fit of the deterministic model, were subsequently incorporated into stochastic mathematical models. These models were employed to represent the dynamics of viral activity during the initial phases of oral CMV infection, with the confirmation of their accuracy achieved through the analysis of clinical shedding data. The research revealed that transient oral CMV infections, marked by low-level shedding, were more prevalent than fully established primary infections.

There also have been efforts aiming to leverage the advantages of deterministic and stochastic approaches to present a more complete picture. In Gong Y [27], the authors modeled CMV dynamics in the dam compartment using a deterministic ODE system, in the placenta compartment using a deterministic PDE equation to capture spatial movement of the viruses, and in the fetus compartment using stochastic models due to the low viral count. Their findings suggest that maternal CD4+ T cells play a critical role in preventing severe congenital CMV disease, with the model showing that the extent of immune suppression significantly influences transplacental transmission risk, and that hyperimmune globulin (HIG) infusion is most effective when administered within two weeks of maternal infection. Furthermore, the risk of congenital CMV is higher during later trimesters of pregnancy due to placental growth, and preexisting immunity to CMV reduces the risk of transmission in reactivated chronic maternal infection compared to primary infection.

Integration With Public Health Strategies

A comprehensive set of public health strategies can be implemented to combat CMV transmission effectively.

As an example, to gain insights into vaccine efficacy, the duration of immunity, and how these factors might differ based on CMV serostatus and the age at vaccination, several CMV vaccine programs are currently in development. These pro-grams leverage mathematical models to target specific groups, such as females and young children of both sexes, as high-lighted by authors from the Centers for Disease Control and Prevention (CDC) [28]. In summary, we emphasize several key aspects that warrant implementation. Firstly, targeted pre-transplant screening and education programs should be developed, encompassing CMV aerostats screening for both donors and recipients, alongside educational initiatives to raise awareness of CMV transmission risks among high-risk HCT recipients and donors. Personalized counseling for seronegative recipients can empower them to make informed decisions regarding CMV prevention, including options like antiviral prophylaxis and monitoring. Following transplantation, enhanced post-transplant surveillance and management protocols should be established, focusing on organ-specific risks. Personalized monitoring strategies based on primary infection conditions and latent viral burden can enable early intervention. Moreover, immune-based interventions should be optimized by promoting research on adoptive transfer of virus epitope-specific CD8+ T cells, establishing guidelines for their timing and dosage post-HCT, and educating healthcare providers about the pivotal role of CD8+ T-cell monitoring in CMV management. Minimizing transmission risks in HCT necessitates thorough CMV screening of donors and recipients, exploration of alternative stem cell or marrow sources to reduce transmission risk, and educating transplant teams about the inefficiency of transmission via these routes. Additionally, vector control measures should be implemented to mitigate CMV transmission by aphids, including surveillance of aphid vector density and collaboration with relevant agencies. Lastly, timing-sensitive intervention guidelines should be developed to optimize the administration of interventions such as hyperimmune globulin (HIG) infusion, especially within two weeks of maternal infection during pregnancy, with health- care providers, particularly obstetricians, being educated about the importance of timing in reducing congenital CMV risk. Implementing these strategies holistically can substantially enhance CMV prevention and control efforts, benefiting high- risk populations and the wider community.

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