Modelling within-host mechanisms underlying the control of acute measles infection in presence of variations in infection doses

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Introduction

The progression of viral infections can vary depending on the initial number of infectious viral particles. Our understanding of the impacts of infection doses on virus-host interactions is currently limited due to challenging practical constraints, and a lack of research. This is important in the context of measles, since measles is a highly transmissible rash disease perturbing the immune system, and a leading cause of childhood morbidity and mortality.

Here, we investigated mechanisms underlying measles infection dose responses. We build on previous animal and mathematical studies from [1-3].

Methods

Animal studies:

- Wild-type Bilthoven measles virus strain (MV-BIL)
- Infection by the respiratory route
- 10000, 1000, 100, 10, 1, and 0.1 Tissue Culture 50% Infectious Dose ($TCID_{50}$)
- 14 cynomolgus monkeys, 3 monkeys per dose on average
- Monitoring the first 18 days post infection
- Longitudinal data on Peripheral blood mononuclear Cells (PBMC) associated infectious viremia

Ordinary Differential Equations (ODEs) in Fig. 1 describe:

- MV infection of lymphocytes, including MV-specific activated T cells
- Virus-to-cell infection with mass-action process
- No MV-induced lymphocyte death
- Release of new MV particles via virus budding from the membrane of infected lymphocytes
- Michaelis-Menten proliferation of MV-specific activated T cells
- Mass-action cytolytic killing of infected lymphocytes by activated MV-specific T cells
- No effects from antibodies

Model-data fitting using maximum likelihood estimation

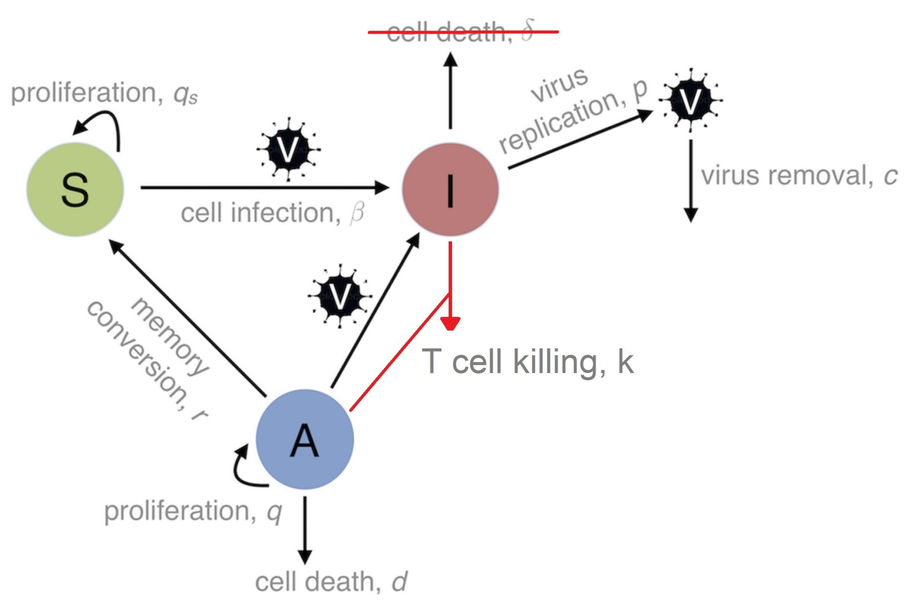

Figure 1: Diagram describing ordinary differential equations modelling acute measles infection
"V" refers to cell-associated measles infectious viremia, "S" refers to susceptible lymphocytes, "I" refers to mV-infected lymphocytes, and "A", refers to MV-specific activated T cells. Original image from [2]

Results:

1) Good description of the data by the model (Fig. 2 A)
2) Dose-independent magnitude of the peak viremia (Fig. 2 A)
3) Dose-dependent changes in the timings of acute viremia (Fig. 2 A)
4) The lower the MV infection dose, the later acute MV infection (Fig. 2 A)
5) The lower the MV infection dose, the lower the initial cell-associated viremia, and the lower the initial number of activated MV-specific T cells (Fig. 2 B1 & B2)
6) The lower the initial number of activated MV-specific T cells, the earlier the peak viremia (Fig. 2 B3)
7) Dose-dependent changes for MV-specific T cell killing (Fig. 2 C)
8) The lower the MV infection dose, the later the drop in the lymphocyte count, without changes in magnitude (Fig. 2 D)

Conclusions

I. Measles infection dose responses are determined by virus-host interactions at the start, along with adaptive and robust control of acute viremia by cellular immunity
II. When MV infection dose decreases, the dose-dependent reduction of MV uptake and immune cell activation increase the time it takes for T cell killing to be sufficient, thereby delaying lymphocyte depletion, clearance of acute viremia, and associated clinical manifestations
III. Support measles prevention, vaccination, and early treatment

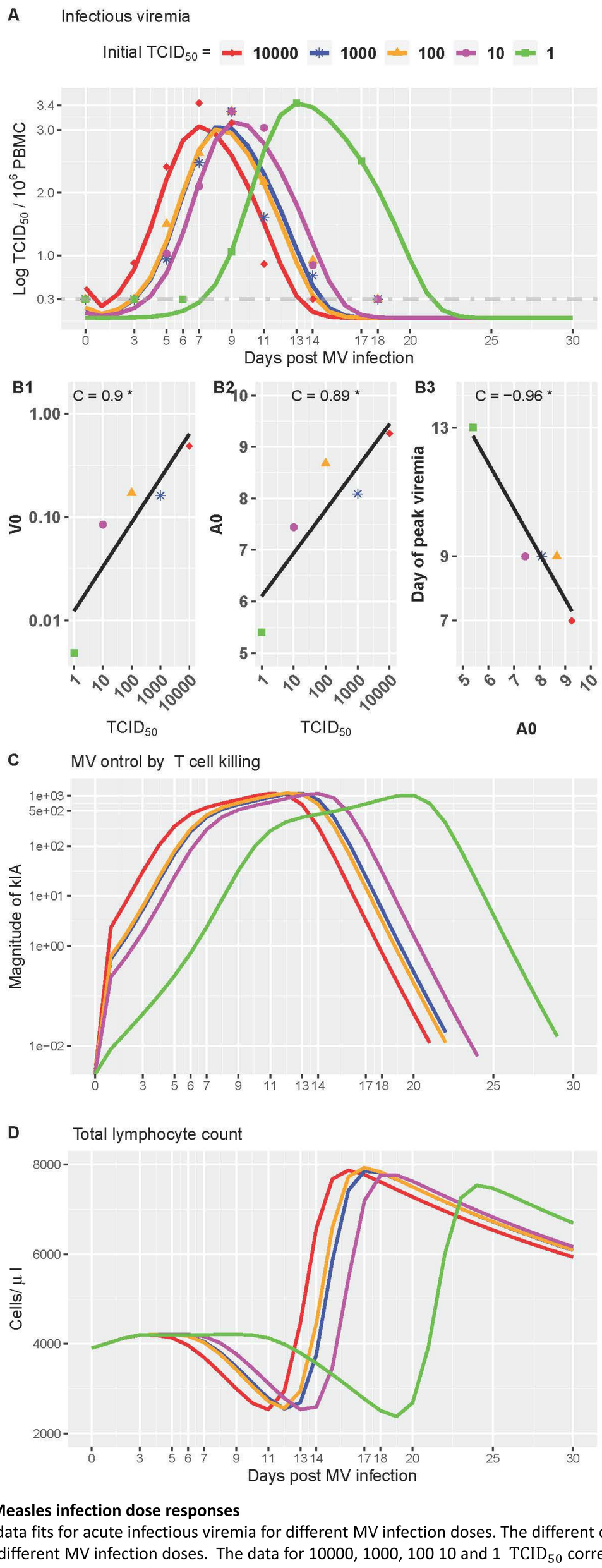

Figure 2: Measles infection dose responses
A: Model-data fits for acute infectious viremia for different MV infection doses. The different colors represent different MV infection doses. The data for 10000, 1000, 100 10 and 1 $TCID_{50}$ correspond to red diamonds, blue stars, orange triangles, magenta dots, and green squares respectively. The solid lines represent the trajectories generated by the model. The dark grey dotted dashed line represents the limit of detection < 0.3, and the viremia for MV infection dose 0.1 $TCID_{50}$. Data from macaque studies in [1]
B1: Relationship between MV infection dose and the estimated infectious viral load on day 0, V0, "C" demotes the correlation coefficient, and "*" refers to the significance level for p-values less than 0.05
B2: Relationship between MV infection dose and the estimated number of activated MV-specific T cells on day 0, A0
B3: Relationship between the estimated number of activated MV-specific T cells, A0, and the day of the peak of acute viremia from the data
C: Simulation of the **t**ime course of the MV-specific T cell killing, kIA, for different MV doses
D: Simulation of the time course of the total lymphocyte count, (L=S+I+A), for different MV doses

References

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[2] MORRIS, Sinead E., et al. Modeling the measles paradox reveals the importance of cellular immunity in regulating viral clearance. PLoS pathogens, 2018, 14.12: e1007493
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