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WORK IN PROGRESS

WP16- How to prevent viremia rebound in virus infections?

Evidence from a data-driven mathematical model for PRRS

By Andrea Doeschl-Wilson, Natacha Go and Suzanne Touzeau

Vaccines can drastically alter the environment in which pathogens live. Indeed, the goal of vaccination is not only to protect individuals from disease, but to decrease the risk and severity of disease outbreaks in populations, and ultimately to eradicate the disease. For the porcine reproductive respiratory syndrome (PRRS), one of the most devastating pig diseases in the world and endemic in most European countries, vaccination has so far proven ineffective in controlling the disease. Indeed, the fast evolving, highly genetically diverse PRRS virus poses a real challenge for developing fully protective vaccines with long-term effectiveness.

SAPHIR WP16 uses mathematical modelling and statistical inference to develop predictive models to assess epidemiological and evolutionary consequences of vaccination for livestock diseases such as PRRS. The results of these models can help researchers and vaccine producers within and outside SAPHIR to develop safer and more effective vaccines, and farmers and policy makers to develop vaccination programmes that keep pig farms PRRS free long-term.

One of the big challenges in vaccine development and infection control is that not all animals respond the same way to infection or vaccination, and that the response is

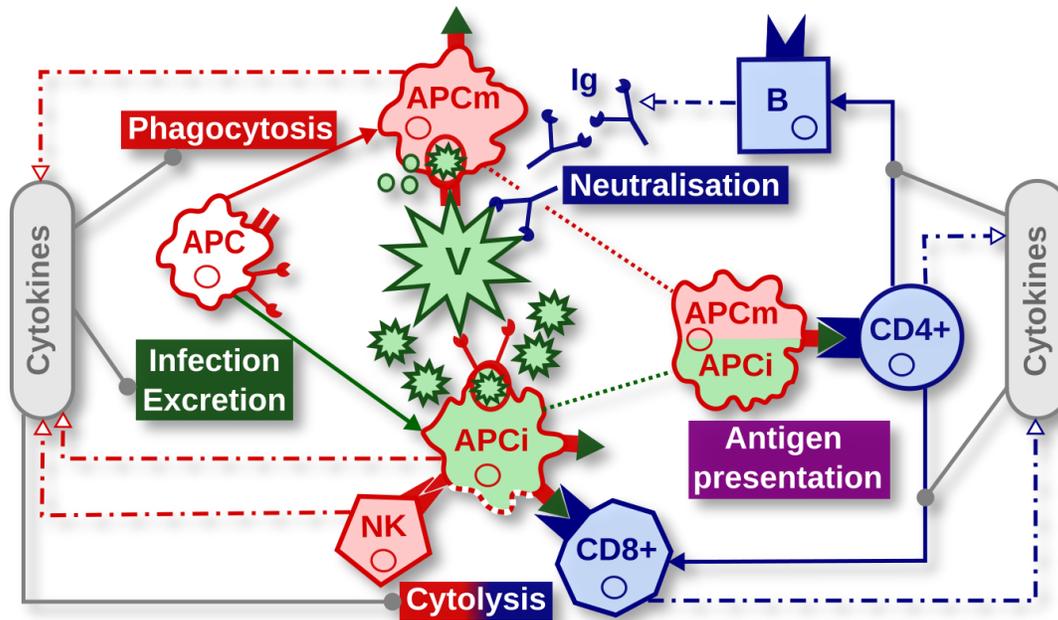


Figure 1: Functional diagram of the model representing the within-host immune response to PRRSv infection.

Binding of PRRS viral particles (V) and naive target cells (APC) either result in mature and non-infected cells (APCm) that phagocytose viral particles, or in mature and infected cells (APCi) that allow viral replication and excretion of new viral particles. Viral particles are neutralised by antibodies (Ig); infected cells are cytolysed by natural killers (NK) and cytotoxic lymphocytes (CD8+). Mature target cells (APCm and APi) present the viral antigen to naive adaptive effectors (CD4+) which activate the CD8+ and B lymphocytes (B). B cells synthesise antibodies. Cytokines are synthesised by various effectors (APCm, APi, NK, CD4+, CD8+) and regulate most of the immune mechanisms (phagocytosis, infection, excretion, antigen presentation, cytolysis). Regulations are either activation, amplification or inhibitions.

Colours – green: PRRSv particles; red: innate response; blue: adaptive response; purple: both innate and adaptive responses.

Lines – plain with arrow: state changes; dashed (dotted) with arrow: (cytokine) syntheses; plain dark grey with bullet: regulations by cytokines.



strain-dependent. In particular, virus load rebound following a steady phase of viral decline (see *Figure 2*) is a common and highly undesirable phenomenon for PRRSv and other viral infections across a range of species. These rebounders not only suffer prolonged infection themselves, but are also likely to maintain the disease in the herd for longer. **What causes some individuals to experience viremia rebound while others manage to steadily clear the virus?**

profiles but also offers, for the first time, insight into potential causative immune mechanisms for generating rebound. In particular, contrary to current hypotheses emerging from genetic analyses, this model reveals that viremia rebound can occur as a result of between-host differences in the immune competence alone, without the commonly hypothesized emergence of viral escape mutants.

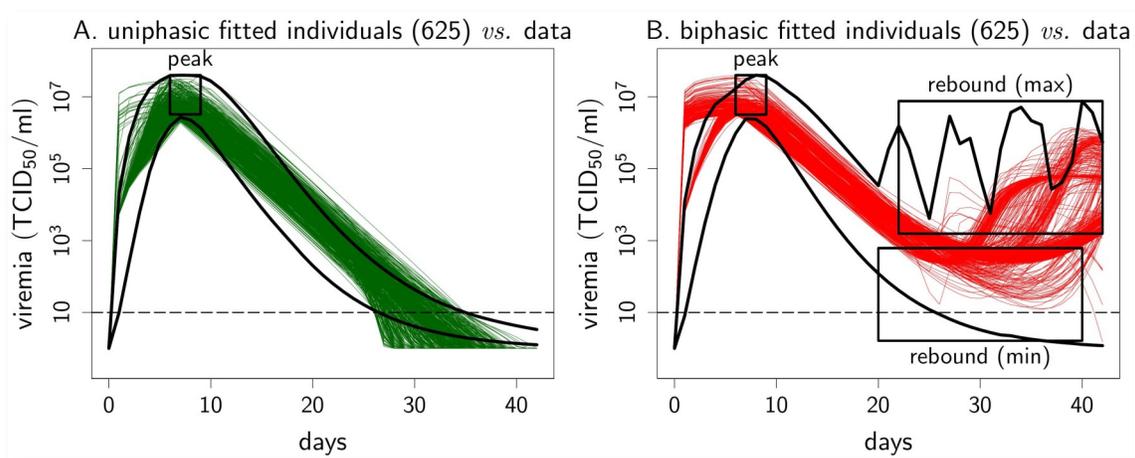


Figure 2: Modelled viremia profiles compared with the data (lower and upper envelope: black curves) for the A. non-rebound, uniphasic profiles (green) and B. rebound, biphasic (red) profiles.

Black boxes: data ranges for the first viral peak, the rebound peak (max) and the minimum between the two peaks (min). Dashed line: viremia detection threshold. Semi-log graphs.

To determine whether rebound can be caused by differences in the immune response alone, researchers from INRA, Inria, France and The Roslin Institute, UK created a mathematical model of PRRS within host infection dynamics (see *Figure 1*) and fitted it to a dataset from a large scale experiment (see *Figure 2*), in which thousands of genetically diverse pigs were challenged with a virulent PRRS virus strain (courtesy of the PRRS Host Genetics Consortium). This mechanistic infection model, fitted to the experimental data, not only successfully reproduced the observed wide range of viremia

Amongst the identified candidate immune mechanisms, the data-informed model revealed that rebound is promoted by high target cell apoptosis, high cell infection and low cytolysis of infected cells by cytotoxic lymphocytes, while increasing virus neutralisation efficiently prevents rebound. The model results suggest that vaccines or genetic selection promoting strong neutralising and cytolytic responses, ideally associated with low apoptotic activity and cell permissiveness, would prevent rebound.

Cytotoxic lymphocytes and neutralising antibodies are usual targets for vaccine development. However, given the

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high diversity of circulating PRRSv strains, cross-protection remains a major challenge for PRRSv vaccination. Consequently, alternative solutions that target non-specific immunity, in particular those leading to lower target cell permissiveness and/or reduced apoptotic activities are particularly relevant. Non-specific immunity can originate from host intrinsic, genetically driven, innate immune responses or from alternatively trained immunity. This non-specific alternatively trained immunity could result from attenuated vaccines against other pathogens, as shown in infants, or could be explicitly elicited by immunostimulants such as those indicated by the model (such as TNF α) or others yet to be defined.

The research was carried out as a collaboration between SAPHIR, MIHMES, an INRA led multi-scale modelling project (<https://www6.inra.fr/mihmes>), and the PRRS Host Genetics Consortium (PHGC). The authors would like to thank the SAPHIR coordinator Isabelle Schwartz for her constructive comments to this article.

“...rebound and thus possible prolonged virus transmission in a pig herd can be prevented by altering the immune response through vaccines or other pharmaceuticals.”

The findings of this theoretical study have profound consequences for the development of successful PRRS intervention strategies, as they would imply that rebound and thus possible prolonged virus transmission in a pig herd can be prevented by altering the immune response through vaccines or other pharmaceuticals. The identified immune mechanisms for preventing rebound could also help to identify pig genes associated with prolonged virus transmission.