A simple mechanistic explanation for original antigenic sin and its alleviation by adjuvants

SUPPLEMENTARY TABLE AND FIGURES

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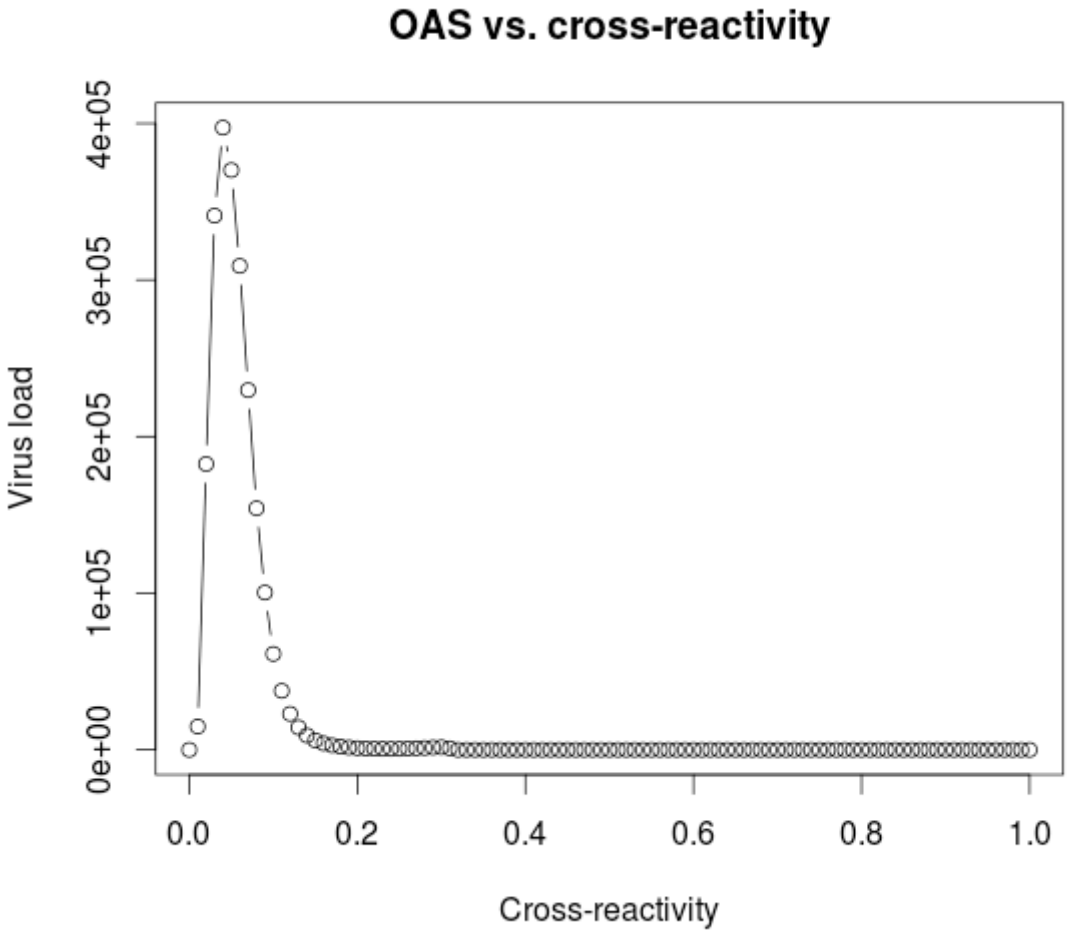
21 **Table S1. Variables and parameters of the mathematical model**

Variable or parameter	Definition (units)	Value (Ref.)
V	Infectious virus titer (EID_{50}/ml)	Measured [1]
E^-	No. uninfected target cells	Calculated
E	No. infected target cells	Calculated
R	No. activated Treg cells	Calculated
B	No. activated B cells	Calculated
A	IgG titer in serum (pg/ml)	Measured [1]
D	Antigen dose loaded by dendritic cells	Calculated
A(0)/B(0)/ E(0)/R(0)/ D(0)	Initial values of indicated variables	0
$E^-(0)=E_0$	Initial no. uninfected target cells	2e5 [1]
V(0)	Initial concentration of infecting virus (EID_{50}/ml)	1.5e3 [1]
p_E	Renewal rate of target cells (day^{-1})	1e-3 [1]
c_V	Rate of nonspecific virus clearance (EID_{50}/ml/day)	4 [1]
β_E	Infection rate of target cells (ml/EID_{50}/day)	5e-6 [1]
ϵ_V	Production rate of infectious virus per infected target cell (EID_{50}/ml/day)	1e2 [1]
b_B /b_R	Max. activation rate of naive B/Treg cells (day^{-1})	3 [2]
p_B /p_R	Max. proliferation rate of B/Treg cells (day^{-1})	8e-1
ϵ_A	Production rate of IgG antibody by B cells	6e-2 [2]
δ_B /δ_R	Death rate of B/Treg cells (day^{-1})	1e-1 [2]
δ_E	Death rate of infected epithelial cells (day^{-1})	1.2 [1]
δ_A	Clearance rate of IgG antibody (day^{-1})	4e-2 [2]
s	Avg. no. antibodies for virus neutralization	3 [3]

q	Avg. no. dendritic cell-loaded antigens for lymphocyte activation	1
c_A	Rate constant for virus neutralization by IgG (ml/pg/day)	1e2
τ_n/τ_a	Antigen dose for half-maximal (re)activation of naïve/pre-activated Treg cells	1e-1/1e-2*
η_n/η_a	Antigen dose for half-maximal (re)activation of naïve/pre-activated B cells	1e-1/1e-2*
λ	Antibody concentration for half-maximal neutralization of virus (pg/ml)	1e3
β_D	Rate of antigen loading by dendritic cell (ml/EID_{50}/day)	1e-3
k_R	Rate of antigen de-loading by dendritic cell under the influence of Treg cells (day^{-1})	1e-1

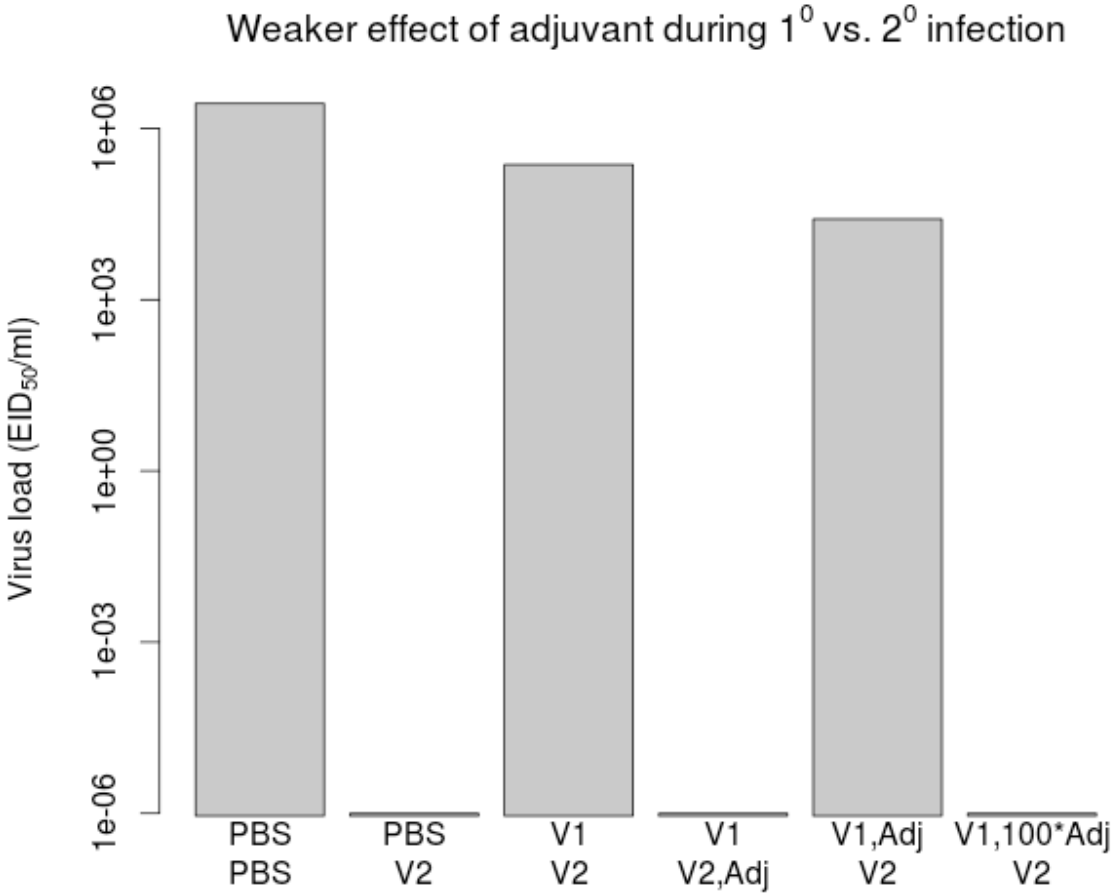
*Previously activated lymphocytes have much lower (re)activation thresholds than naive lymphocytes [4].

Figure S1



OAS peaks at intermediate cross-reactivity. I simulated the sequential infection of mice by 1500 EID_{50}/ml of strain V1 followed 28 days later by the same amount of a cross-reacting strain V2, while varying the cross-reactivity between both strains from 0 to 1. I then simulated a challenge infection by V2 occurring 28 days after the last infection. I plottedthe peak amount of V2 that was produced in each challenged mouse (calculated as the peak virus load minus the challenge dose) as a function of cross-reactivity.

Figure S2



Adjuvants are less effective when given during the first infection. I simulated the sequential infection of mice by 1500 EID50/ml of strain V1 followed 28 days later by the same amount of a cross-reacting strain V2 (cross-reactivity σ=10%). I then simulated a challenge infection by V2 occurring 28 days after the last infection, after infection by V2 alone (immune control), and after no prior infection (naïve control). I simulated the injection of mice with dendritic cell-activating adjuvants during infection by V2, by increasing the rate at which dendritic cells load antigens from an initial value of 10-3 ml/EID50/day to either 10-1 ml/EID50/day (denoted Adj in the plot) or 10 ml/EID50/day (denoted 100*Adj). I plotted (on a log-scale) the peak amount of V2 that was produced in each challenged mouse (calculated as the peak virus load minus the challenge dose).. As in the text, I use “PBS” to denote the absence of a first (respectively second) infection. Strikingly, a simulated 10 fold increase in adjuvant strength confers a sterilizing immunity against the challenge infection

when administered during the second infection, but has a more modest effect during the first infection. Compared to the second infeciton, a much stronger adjuvant is needed during the first infection in order to produce a sterilizing immunity against the challenge infection.

References

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