Supporting Information

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SI Alternative Models

To examine the robustness of our results, we considered the fits of three alternative models.

i) The shared-parameter model has the same underlying structure as the standard model; however, instead of fitting the model to each animal separately, we assume that all parameters except k_T (the inhibitory effect of T cells on MeV) have the same value for all animals. This dramatically reduces the number of parameters but still leads to the same qualitative result that T-cell response alone cannot explain the control of viral replication (Fig. S5).

ii) The nonlinear model differs from the standard model in the way it includes the effects of antibodies (abundance of measles virus-specific antibodies [$A(t)$]) and Foxp3 (suppressive activity of Tregs [$S(t)$]). Instead of additively decreasing or increasing the growth rate of the virus (as they do in the standard model), these components now decrease the viral growth rate and the T-cell responses in a multiplicative way. The nonlinear model is given by the following equation:

$$\frac{dV(t)}{dt} = V(t)\left(\frac{r\ R(t)}{1+k_A A(t)} - \frac{k_T T(t)}{(1+f_S\ S(t))}\right)$$

The model shows the same qualitative behavior as the standard model (Fig. S6); that is, the T-cell version of the model cannot explain viral clearance, adding antibodies leads to a strong improvement ($P < 10^{-5}$, likelihood ratio test) of the model fits, and adding FoxP3 leads to a minor improvement of the model fits.

iii) The T-cell saturation model is the same as the nonlinear model, except that it allows the magnitude of the T-cell response to saturate with increasing concentrations of T cells (1):

$$\frac{dV(t)}{dt} = V(t)\left(\frac{r\ R(t)}{1+k_A A(t)} - \frac{k_T T(t)}{(1+f_S S(t))(1+s\ T(t))}\right)$$

Even though the difference between the T-cell and the T cell-AB versions of the model is smaller in this model than in the other models, it still shows the same overall qualitative patterns (i.e., T cells alone are not able to explain the control of viral replication) (Fig. S4).

Overall these models confirm the robustness of the results based on the standard model presented in the main text.

1. Pilyugin SS, Antia R (2000) Modeling immune responses with handling time. *Bull Math Biol* 62:869–890.

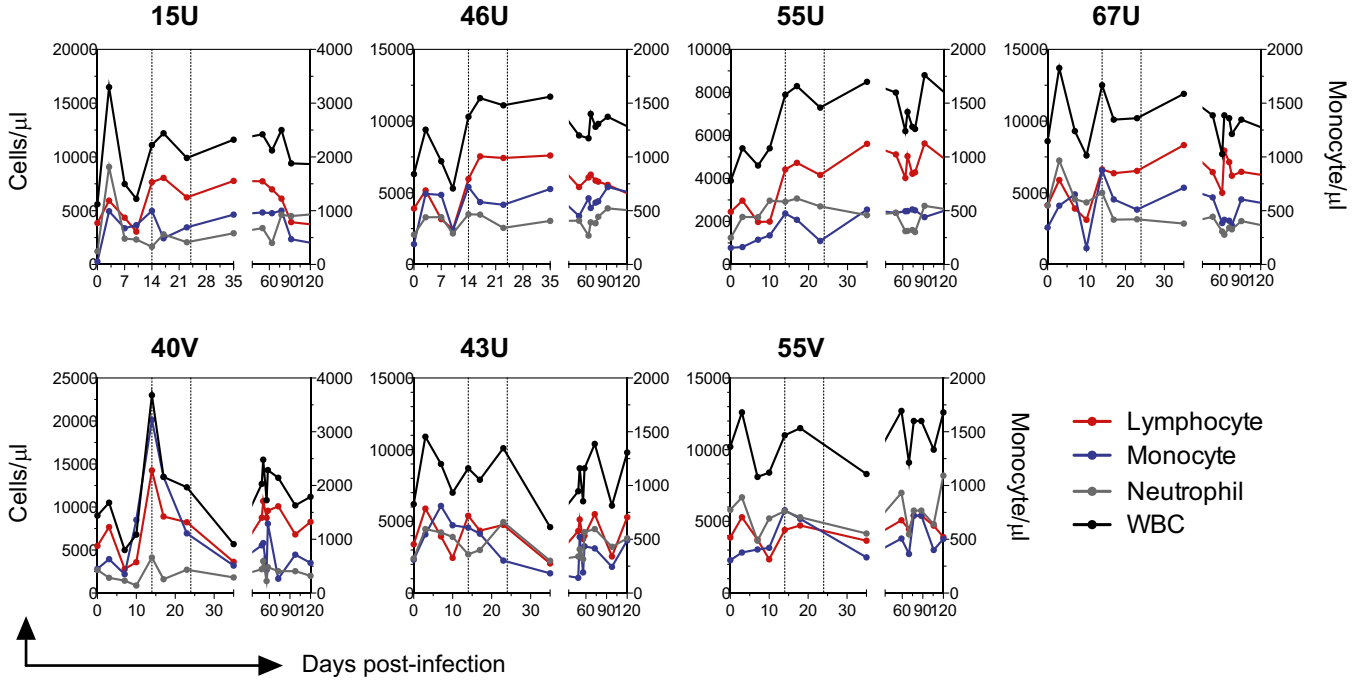

Fig. S1. Change of cell count during measles virus infection. Numbers of lymphocytes (red), monocytes (blue), neutrophils (gray), and total white blood cells (black) per microliter of whole blood determined by an automated cell counter. Numbers of monocytes are plotted against the right *y* axis, and the other three blood cells are plotted against the left *y* axis. Macaques are identified at the top of individual graphs.

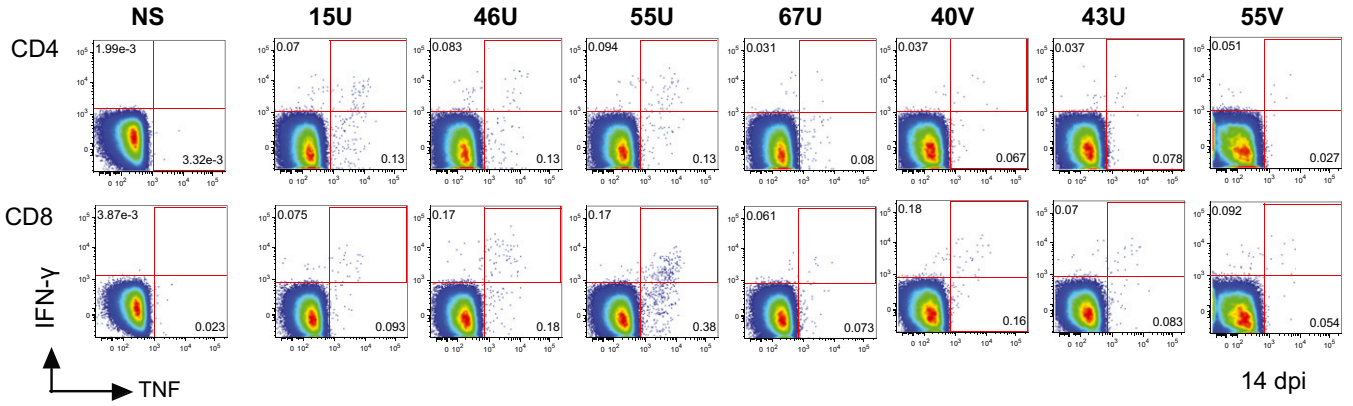

Fig. S2. Measles virus (MeV)-specific CD4$^+$ and CD8$^+$ T-cell responses. Eight-color FACS with intracellular cytokine staining was performed to analyze T-cell function following MeV infection. A total of 1×10^6 fresh peripheral blood mononuclear cells (PBMCs) were stimulated with media alone or pooled hemagglutinin (H) peptides (20-mers overlapping by 11 amino acids; 1 μg/mL) for 12 h and stained for surface markers and intracellular cytokine production. Dot plots of IFN-γ and TNF-producing CD4$^+$ and CD8$^+$ T cells after media alone or H peptide stimulation are shown using PBMCs from macaques 14 d after MeV infection. Macaques are identified at the top of individual graphs. dpi, days post infection; NS, nonstimulated.

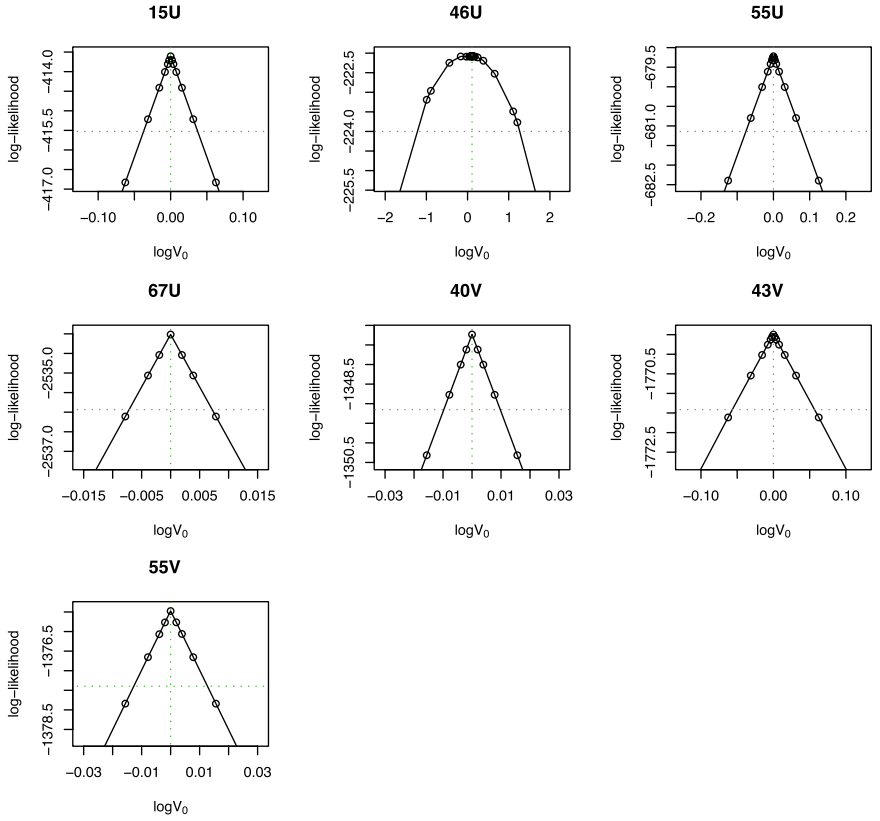

Fig. S3. Likelihood profile 1: Likelihood profile for the initial virus load in the T cell-AB-FoxP3 model. The vertical green line corresponds to the maximum-likelihood parameter estimate. The intersections with the profile and the horizontal green line delimit the 95% confidence interval for that parameter (according to the likelihood ratio test). Note that initial virus load values are restricted to values <1. Therefore, the quantity used for the *x* axes relates to the initial virus load according to V(0) = exp(−Abs(logV_0)) (which explains the peaky likelihood profile). Macaques are identified at the top of individual graphs.

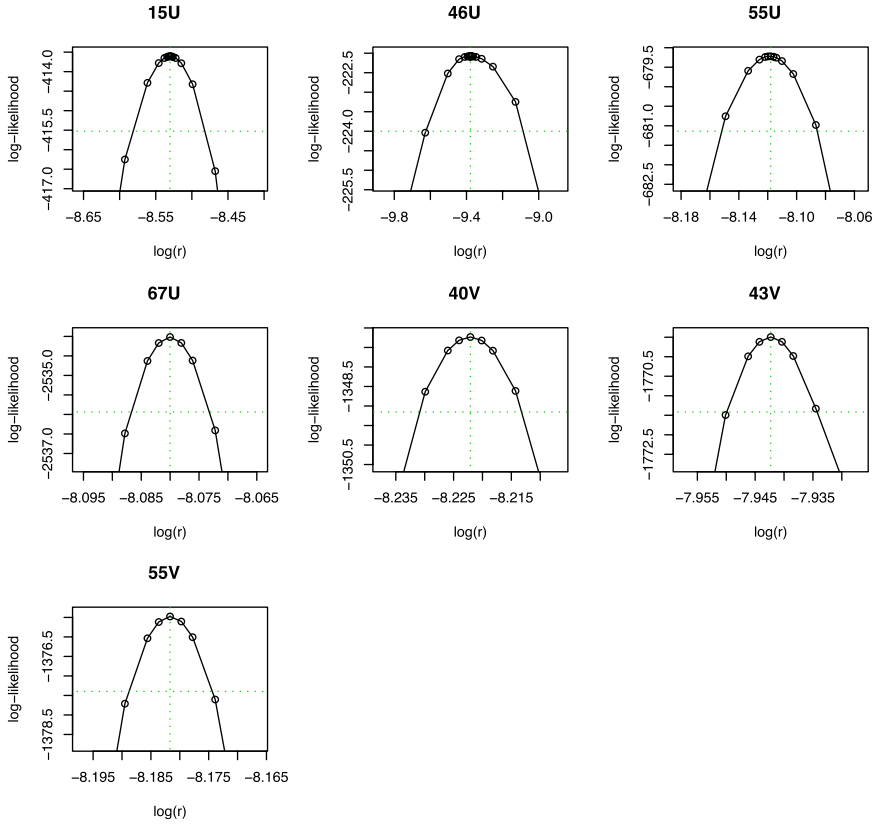

Fig. S4. Likelihood profile 2: Likelihood profile for the parameter *r* (growth rate of the virus) in the T cell-AB-FoxP3 model. The vertical green line corresponds to the maximum-likelihood parameter estimate. The intersections with the profile and the horizontal green line delimit the 95% confidence interval for that parameter (according to the likelihood ratio test). Macaques are identified at the top of individual graphs.

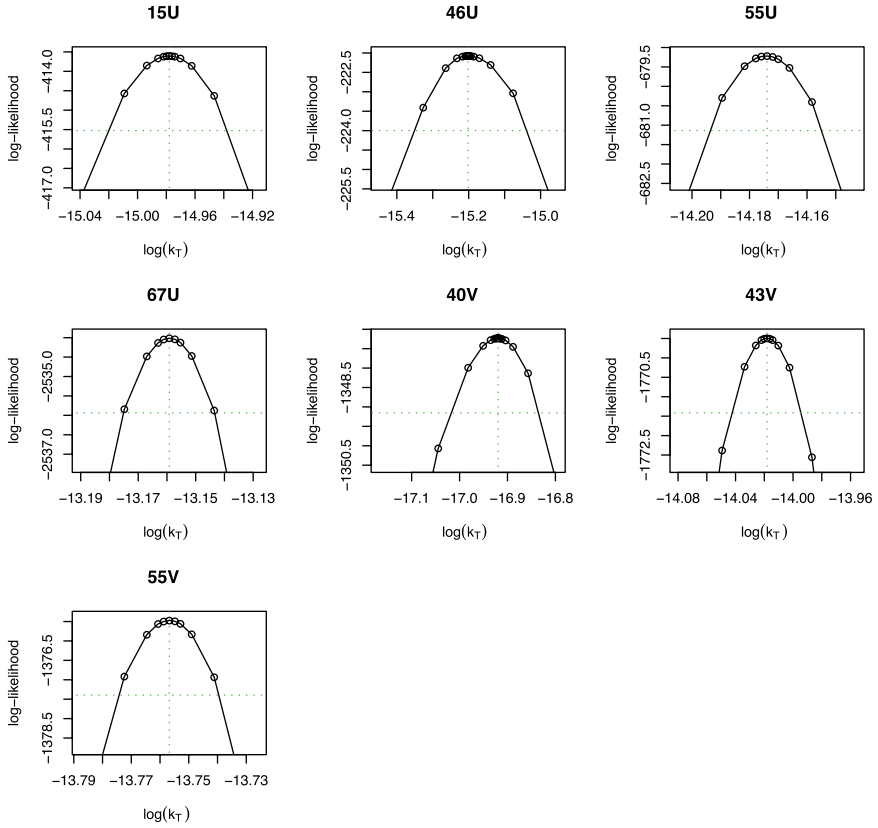

Fig. S5. Likelihood profile 3: Likelihood profile for the parameter k_T (inhibitory effect of T cells on MeV) in the T cell-AB-FoxP3 model. The vertical green line corresponds to the maximum-likelihood parameter estimate. The intersections with the profile and the horizontal green line delimit the 95% confidence interval for that parameter (according to the likelihood ratio test). Macaques are identified at the top of individual graphs.

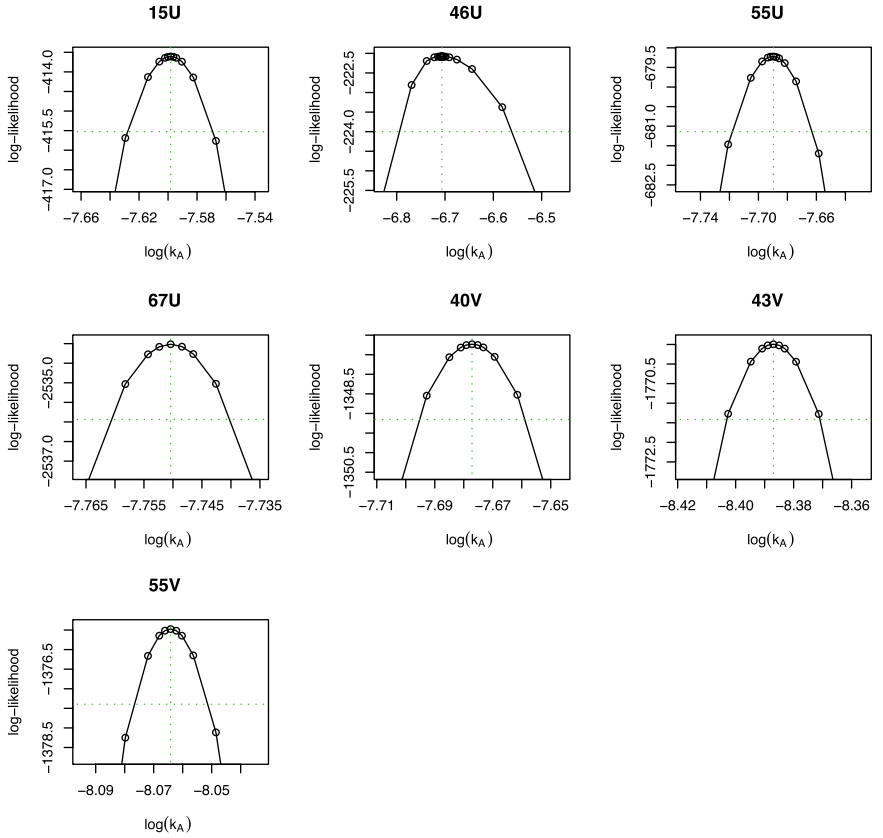

Fig. S6. Likelihood profile 4: Likelihood profile for the parameter k_A (inhibitory effect of antibodies on MeV) in the T cell-AB-FoxP3 model. The vertical green line corresponds to the maximum-likelihood parameter estimate. The intersections with the profile and the horizontal green line delimit the 95% confidence interval for that parameter (according to the likelihood ratio test). Macaques are identified at the top of individual graphs.

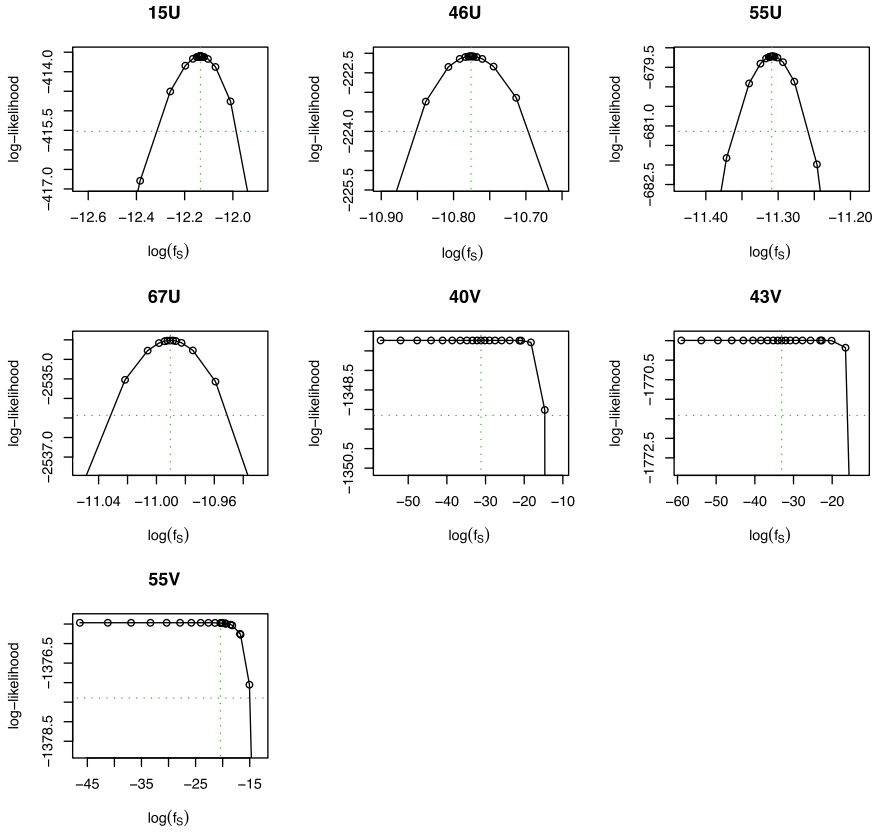

Fig. S7. Likelihood profile 5: Likelihood profile for the parameter f_S (immunosuppressive effect of Tregs) in the T cell-AB-FoxP3 model. The vertical green line corresponds to the maximum-likelihood parameter estimate. The intersections with the profile and the horizontal green line delimit the 95% confidence interval for that parameter (according to the likelihood ratio test). Macaques are identified at the top of individual graphs.

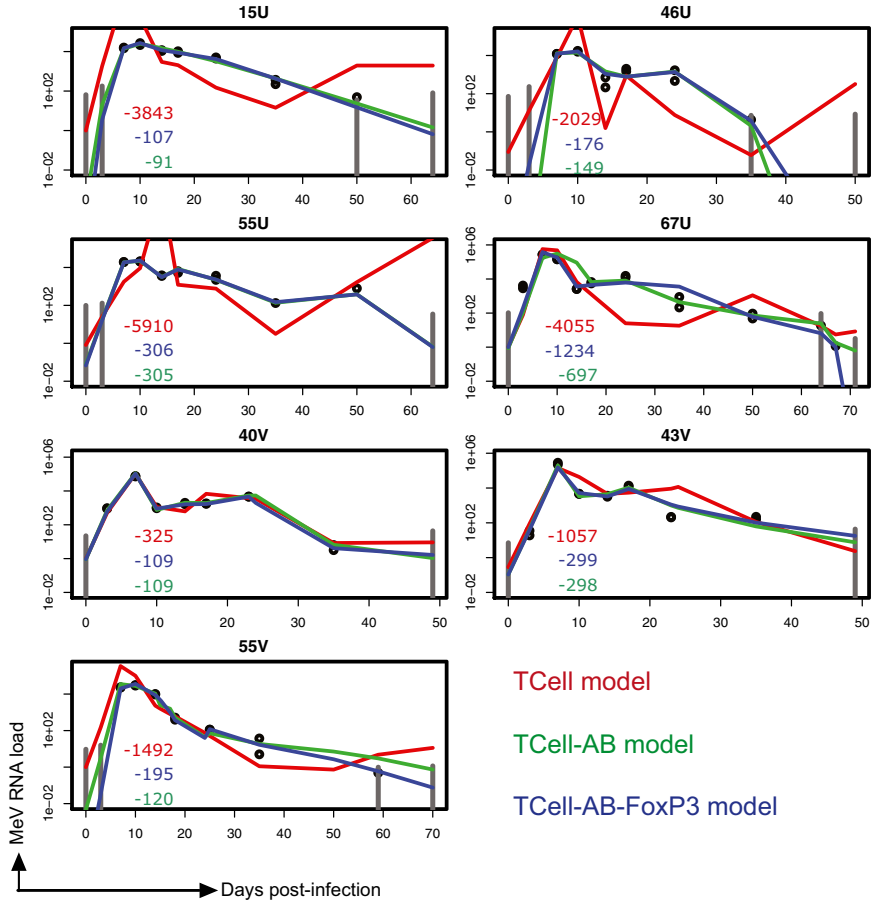

Fig. S8. T-cell saturation model. This model is the same as the nonlinear model, except that it allows the magnitude of the T-cell response to saturate with increasing concentrations of T cells. Colors indicate three different subset models: The T cell-AB model (green line) takes only T cells and antibodies into account, and the T-cell model (red line) takes only T cells into account. The models are fitted for each animal individually. The log-likelihood from the different models is shown, with colors corresponding to lines. The observed measles virus (MeV) RNA load is shown in open circles. Gray vertical lines mark the estimated lowest detection level of the quantitative reverse transcriptase (qRT)-PCR assay at given time points. Macaques are identified at the top of individual graphs.

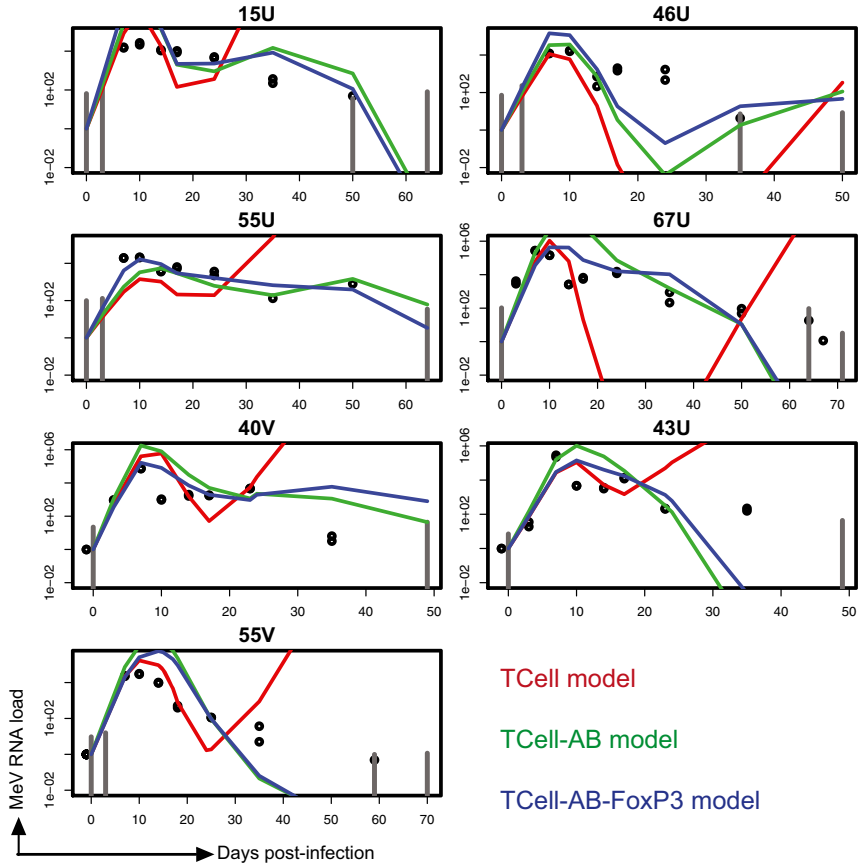

Fig. S9. Shared-parameter model. In this alternative model fit, we fit the standard model to the data but assume that all parameters except k_T (the inhibitory effect of T cells on MeV) are shared between animals. This dramatically reduces the number of parameters. Colors indicate three different subset models: The T cell-AB-FoxP3 model (Eq. **1**; blue line) takes T cells, antibodies, and FoxP3 into account; the T cell-AB model (green line) takes only T cells and antibodies into account, and the T-cell model (red line) takes only T cells into account. The observed measles virus (MeV) RNA load is shown in open circles. Gray vertical lines mark the estimated lowest detection level of the quantitative reverse transcriptase (qRT-PCR) assay at given time points. Macaques are identified at the top of individual graphs.

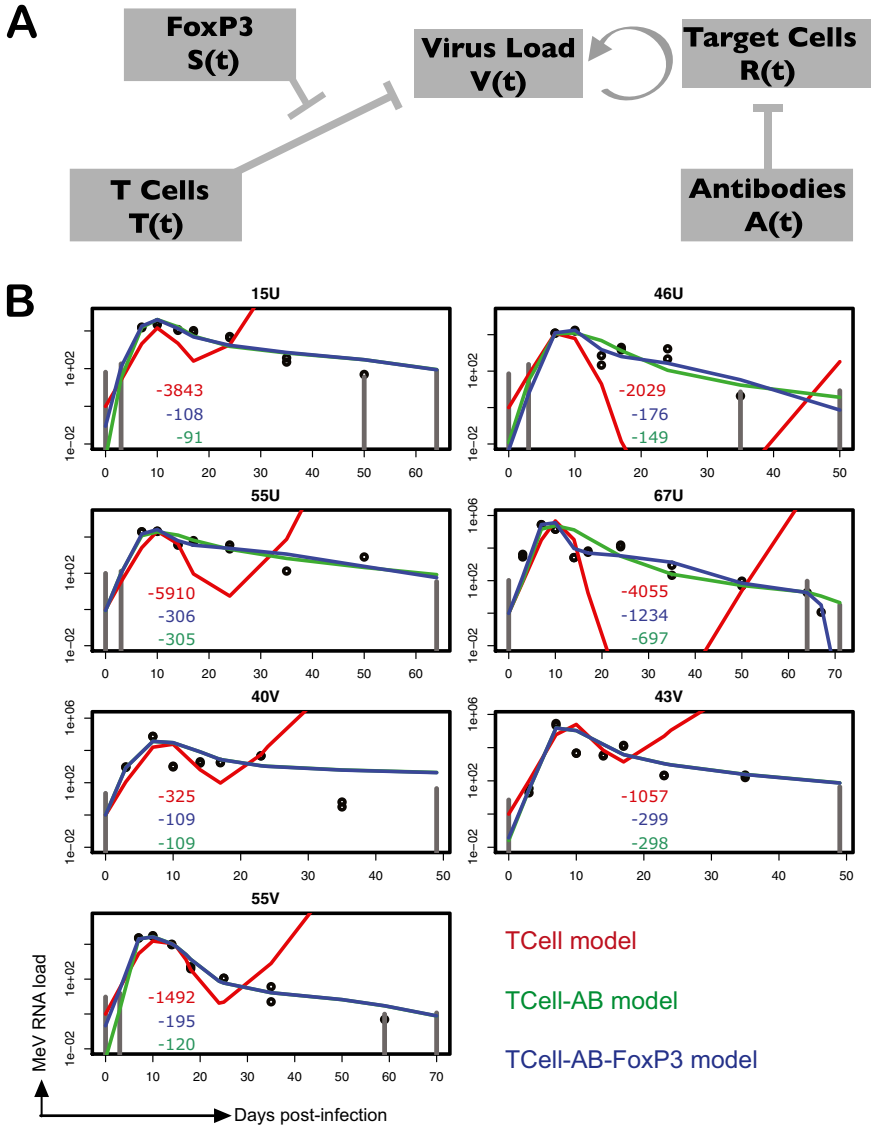

Fig. S10. Nonlinear model. (*A*) Model differs from the standard model (Fig. 3*A*) in the way it includes the effects of antibodies [abundance of MeV-specific antibodies $A(t)$ and FoxP3 suppressive activity of Tregs $S(t)$]. Instead of additively decreasing or increasing the growth rate of the virus (as they do in the standard model), these components now decrease the viral growth rate and the T-cell responses, respectively, in a multiplicative way. (*B*) Colors indicate three different subset models: The T cell-AB-FoxP3 model (Eq. **1**; blue line) takes T cells, antibodies, and FoxP3 into account; the T cell-AB model (green line) takes only T cells and antibodies into account; and the T-cell model (red line) takes only T cells into account. The models are fitted for each animal individually. The log-likelihood from the different models is shown with colors corresponding to lines. The observed MeV RNA load is shown in open circles. Gray vertical lines mark the estimated lowest detection level of the quantitative reverse transcriptase (qRT-PCR) assay at given time points. Macaques are identified at the top of individual graphs.

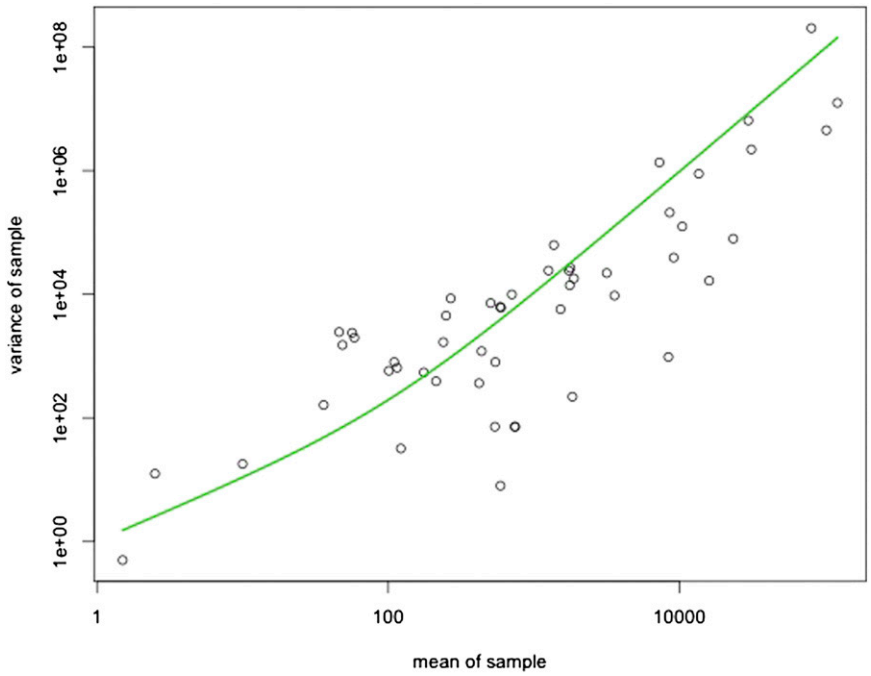

Fig. S11. Mean vs. variance of virus load measurements for each time point. The mean is given by $m_{ti} = 1/2(v_{1,ti} + v_{2,ti})$ and the variance by $Var_{ti} = (v_{1,ti} - m_{ti})^2 + (v_{2,ti} - m_{ti})^2$. The green line corresponds to the mean variance relation expected from the negative binomial distribution that best fits the data.

Table S1. Identification and MHC typing of the study animals

				MHC typing												
Animal ID	Age, y	Sex	Batch	A01	A02	A08	A11	B01	B03	B04	B08	B17	B29	DRB*w201	DRB1*0401/06/11	DPB1*06
15U	2.8	M	1	–	–	–	–	–	–	–	–	–	–	–	–	–
46U	2.7	M	1	+	–	+	–	+	–	–	–	–	–	–	–	–
55U	2.7	M	1	–	+	–	–	+	–	–	+	–	–	+	–	+
67U	2.6	M	1	+	–	–	–	+	–	–	–	–	–	–	+	+
86U	2.2	M	2	–	–	–	–	+	–	–	–	–	–	–	–	+
40V	2.0	M	3	–	–	+	–	–	–	–	–	–	–	+	–	–
43V	2.0	M	3	–	+	–	–	–	–	–	+	–	–	+	–	–
55V	2.3	M	4	–	+	–	–	–	–	–	–	–	–	–	–	–

Eight 2- to 3-y-old male rhesus macaques were infected intratracheally with the Bilthoven strain of measle virus in four batches. MHC typing was performed using a PCR-based assay. M, male.

Table S2. Detection of measles virus RNA in nasal swab samples

ID dpi	3	7	10	14	17/18	23/24	35	50
15U	–	+	+	+	–	–	–	–
46U	–	–	+	+	+	–	–	–
55U	–	+	+	+	+	–	–	–
67U	–	+	+	+	+	+	+	–
40V	–	+	+	–	–	–	n.a.	n.a.
43V	–	+	+	+	+	–	n.a.	n.a.
55V	–	+	+	+	+	+	–	n.a.

Two sterile cotton swabs prewetted in PBS were used to collect secretions and cells from both nares. Cells and fluid were separated by centrifugation. RNA was extracted from the cell pellets. Reverse transcriptase (RT)-PCR was performed using measles virus nucleoprotein-specific primers. RT-PCR products were run on gels and read as positive or negative. dpi, days post infection; n.a., not available.