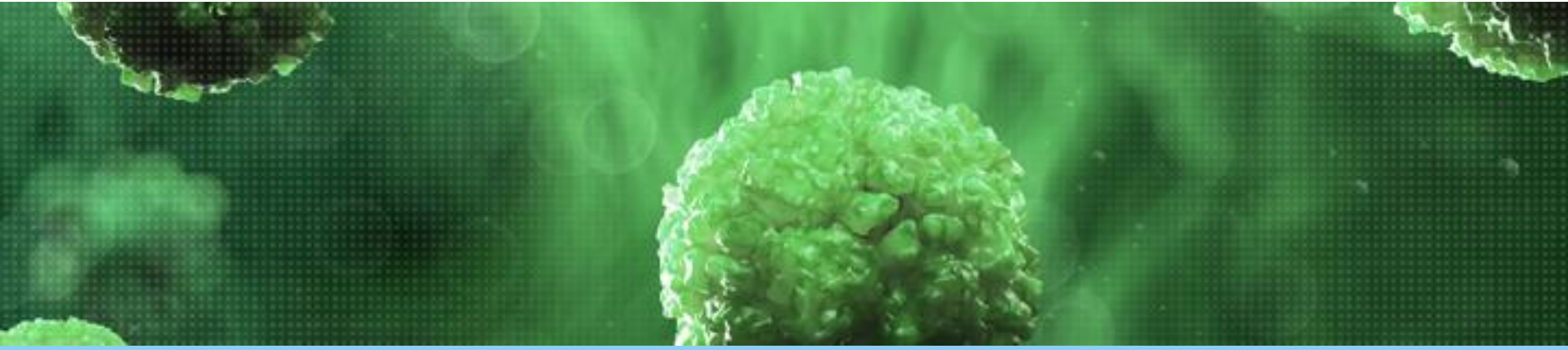
Erasmus MC
University Medical Center Rotterdam

Viroscience lab
WHERE SKILLS MEET TO STUDY & PROTECT



# Immune amnesia following infections with measles virus

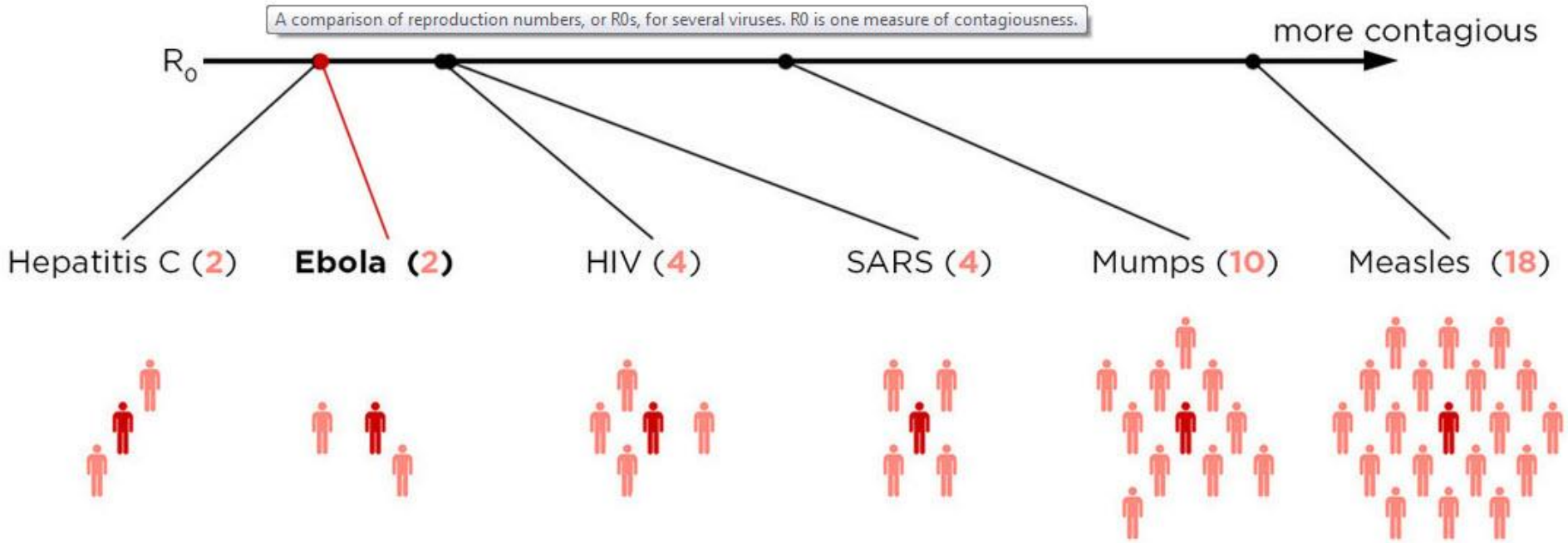
*perspective from a measles outbreak in the Netherlands*

**Rory D de Vries, PhD**
Assistant Professor
Department of Viroscience
Erasmus MC, Rotterdam
the Netherlands

# Measles: the disease

- **Highly infectious:** $R^0$: 12-18

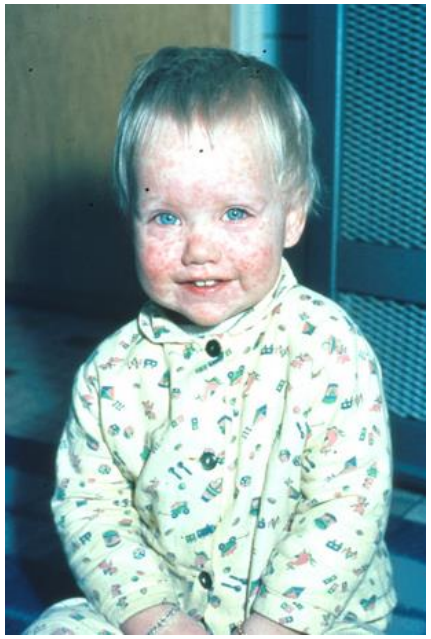
The number of people that **one sick person** will infect (on average) is called $R_0$.
Here are the maximum $R_0$ values for a few viruses.




Erasmus MC
University Medical Center Rotterdam

# Measles: the disease

MEASLES & RUBELLA INITIATIVE | A global partnership to stop measles & rubella



- **Highly infectious:** $R^0$: 12-18
- **Long incubation time:** 9-19 days
- **Symptoms:**
  - rash, fever, cough, conjunctivitis
  - **Immunosuppression:** opportunistic infections

    *e.g. pneumonia, GI tract disease, otitis media*
  - Rare but severe **neurological** complications
- **Estimated global mortality:** 207,500 deaths/yr (2019)


Erasmus MC
University Medical Center Rotterdam

# Cellular receptors for measles virus



letters to nature

SLAM (CDw150) is a cellular receptor for measles virus

Hironobu Tatsuo*, Nobuyuki Ono*, Kotaro Tanaka & Yusuke Yanagi

Department of Virology, Faculty of Medicine, Kyushu University, Fukuoka 812-8582, Japan
* These authors contributed equally to this work

LETTER

doi:10.1038/nature10639

Adherens junction protein nectin-4 is the epithelial receptor for measles virus

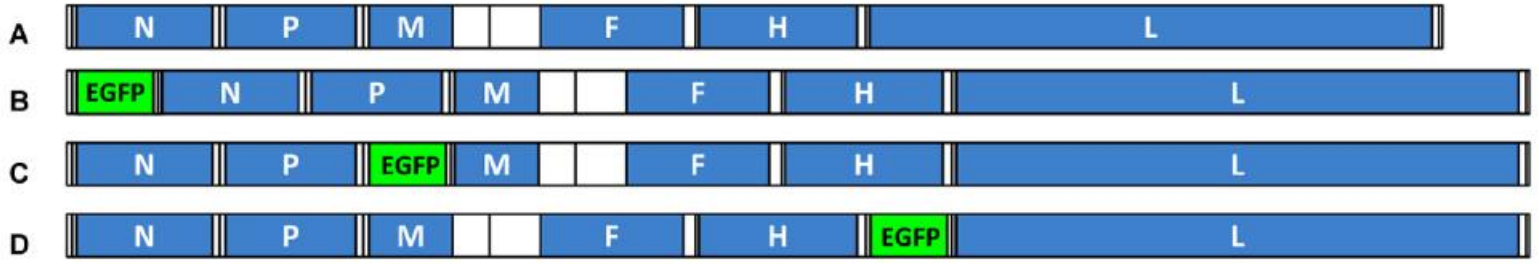
**MV is a Lymphotropic, Myelotropic and Epitheliotropic virus**

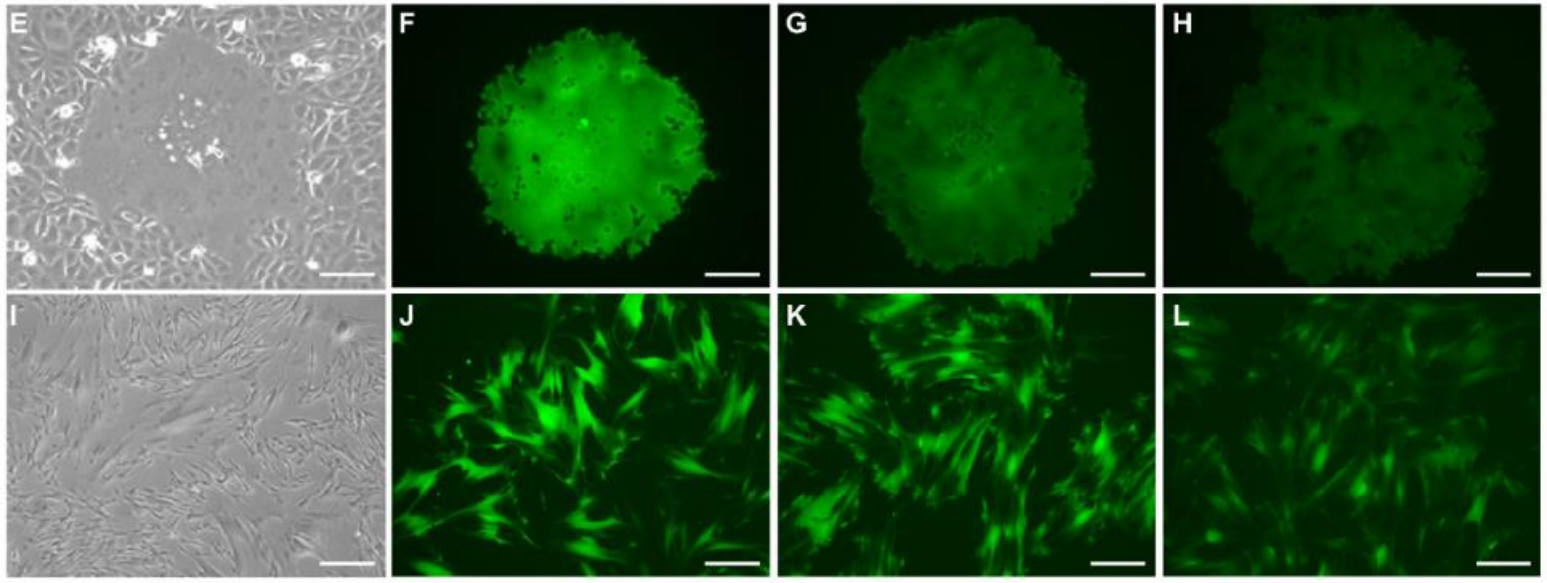
- **2000**: Signalling Lymphocyte Activation Molecule (SLAM, CD150)
  - Expressed on subsets of thymocytes, macrophages, dendritic cells and lymphocytes
- **2011**: Nectin-4
  - Expressed on epithelial cells

Erasmus MC
University Medical Center Rotterdam

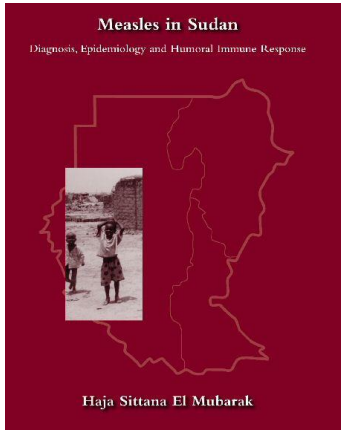
# MV-GFP viruses and animal models

- **Recombinant measles virus:** Khartoum, Sudan (KS)

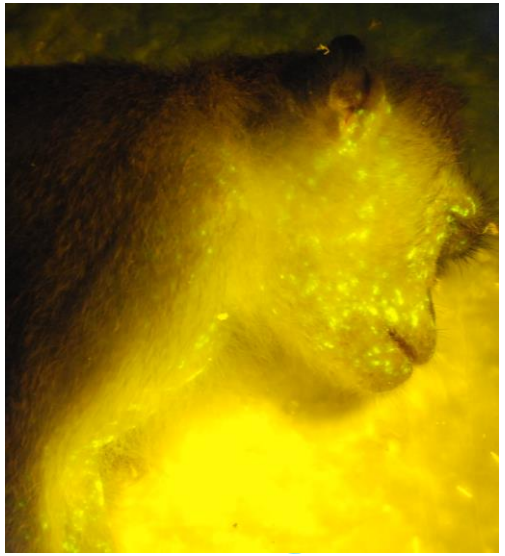



*Lemon et al. PLOS Pathog 2011; Davis et al., CHM 2014*

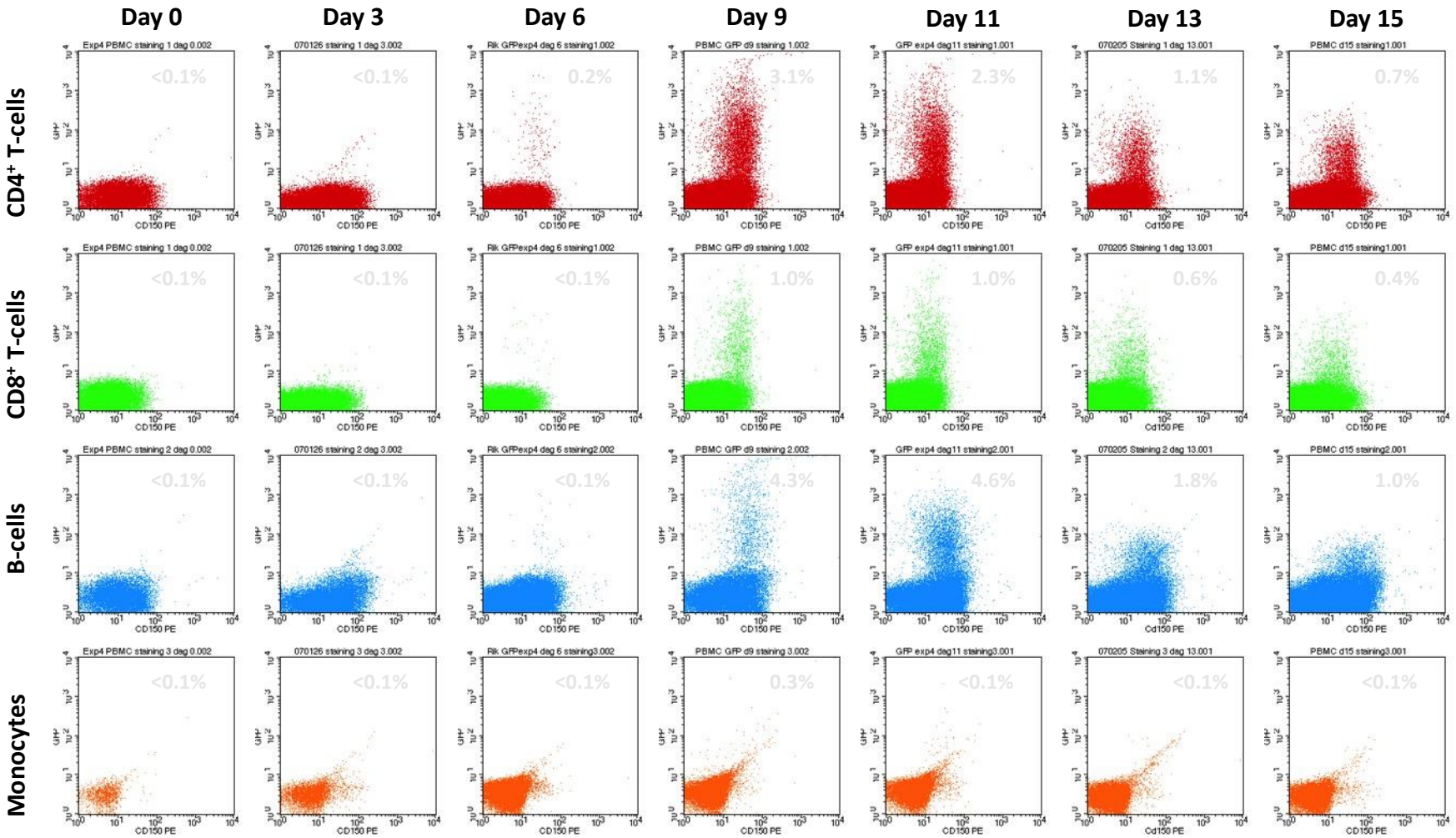



*El Mubarak et al., J Gen Virol 2007*



# Dissemination throughout the host

- Study objective (II): **how is MV disseminated throughout the host?**




Erasmus MC
University Medical Center Rotterdam

# Dissemination via lymphoid / myeloid cells

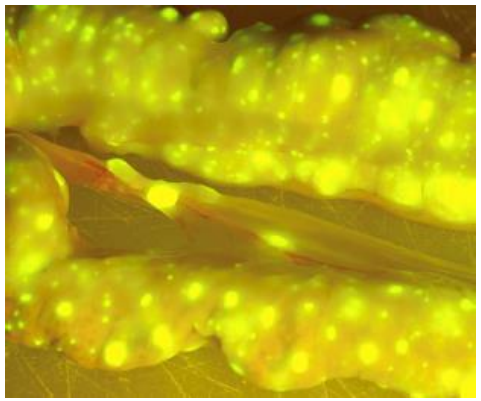
OPEN ACCESS Freely available online PLoS PATHOGENS

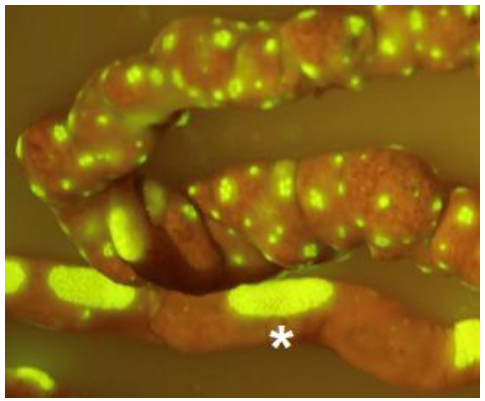
## Predominant Infection of CD150+ Lymphocytes and Dendritic Cells during Measles Virus Infection of Macaques

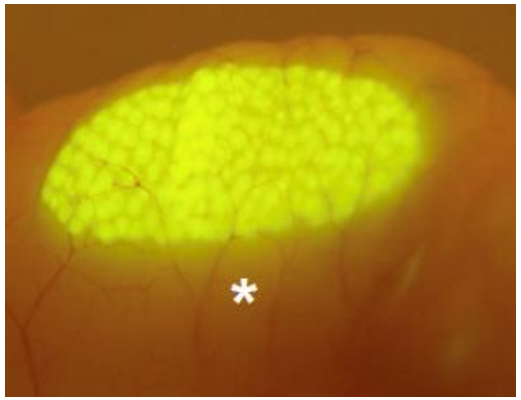
Rik L. de Swart[1*], Martin Ludlow[2☯], Lot de Witte[3☯], Yusuke Yanagi[4], Geert van Amerongen[1], Stephen McQuaid[2], Selma Yüksel[1], Teunis B. H. Geijtenbeek[3], W. Paul Duprex[2], Albert D. M. E. Osterhaus[1]

1 Department of Virology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, 2 School of Biomedical Sciences, Queen's University of Belfast, United Kingdom, 3 Department of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands, 4 Department of Virology, Kyushu University, Fukuoka, Japan

- During peak virus replication MeV mainly targets **lymphoid tissues**
- Massive MeV replication in **submucosal tissues**



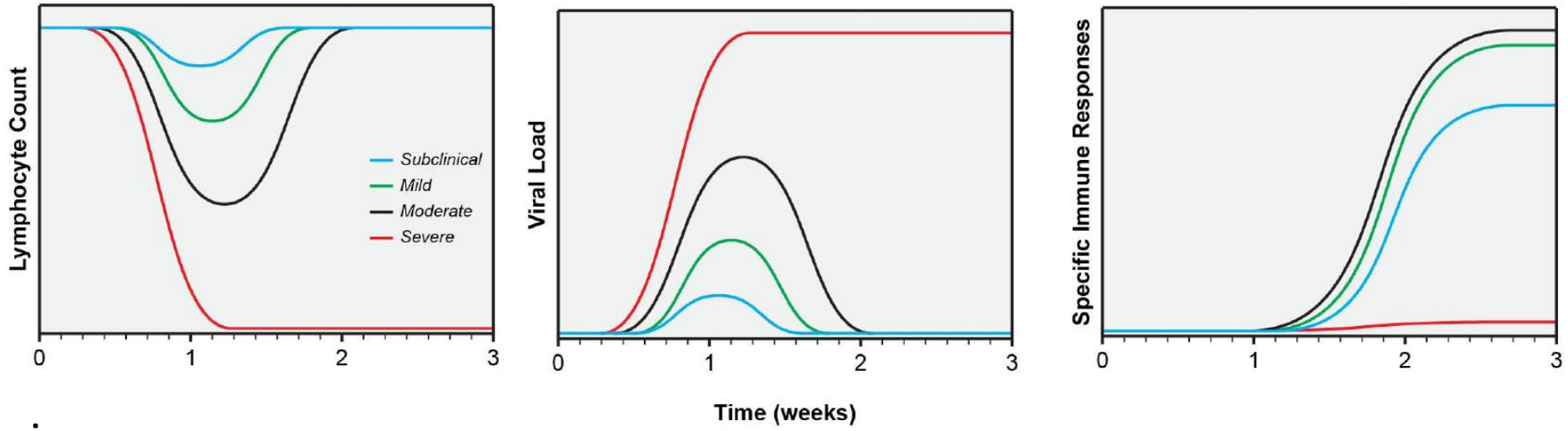




Erasmus MC
University Medical Center Rotterdam

# Measles immune suppression

- Study objective: **characterize mechanism of MV immunosuppression**




- Study design:
  - Percentage MV-infected lymphocytes in blood low (max 1-5%)?
  - Functional impairment of lymphocytes?
  - Functional impairment of antigen presenting cells?

Erasmus MC
University Medical Center Rotterdam

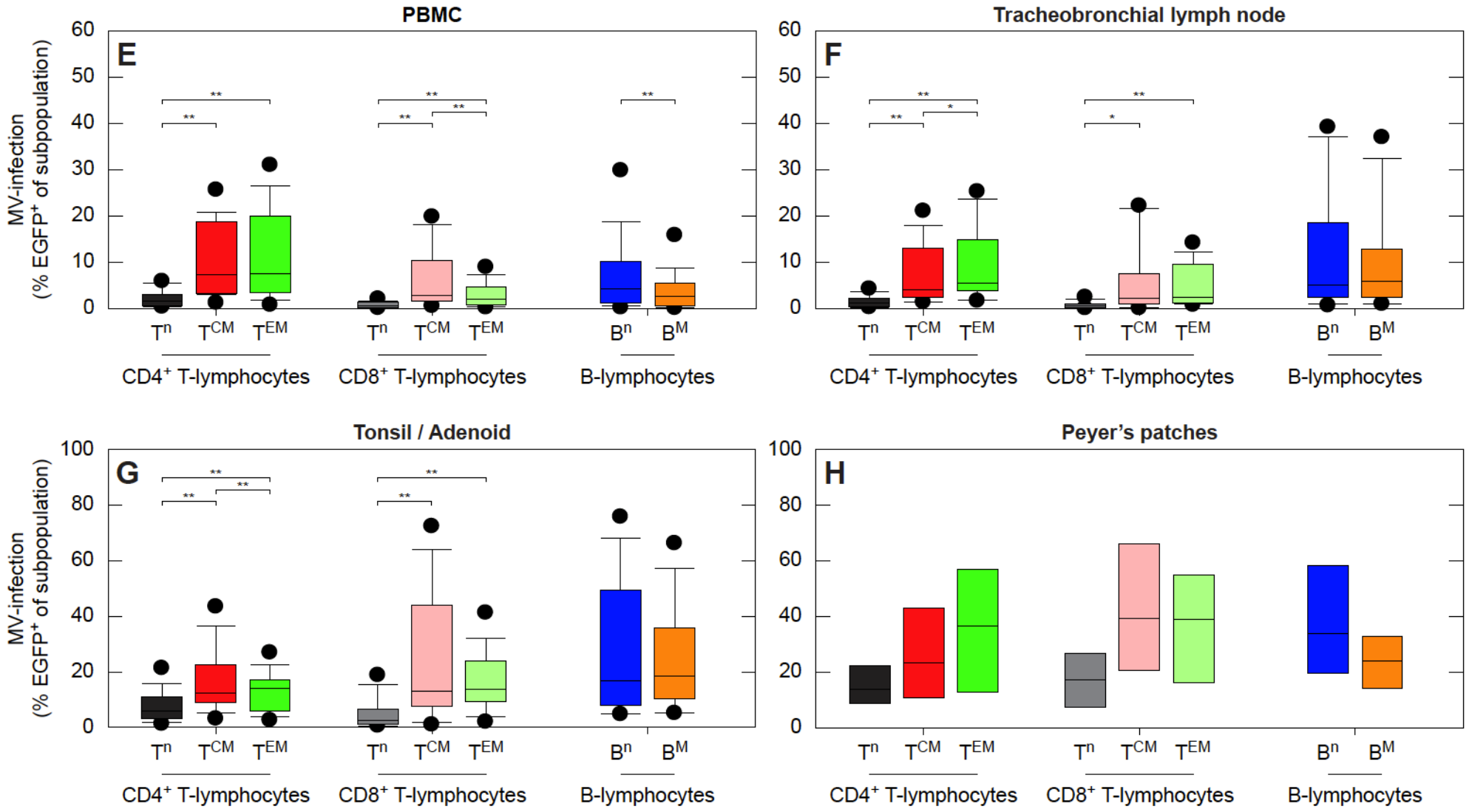
# MV targets lymphoid tissues *in vivo*

- MV infection of lymphocytes is mediated by **CD150**
- CD150 expression is mainly expressed on **memory lymphocytes**
- MV infection in **PBMC** < **lymphoid tissues** < **subpopulations in lymphoid tissues**

- **<u>Hypothesis</u>: infection and subsequent depletion of memory lymphocytes can explain measles immune suppression and increased susceptibility to opportunistic infections**

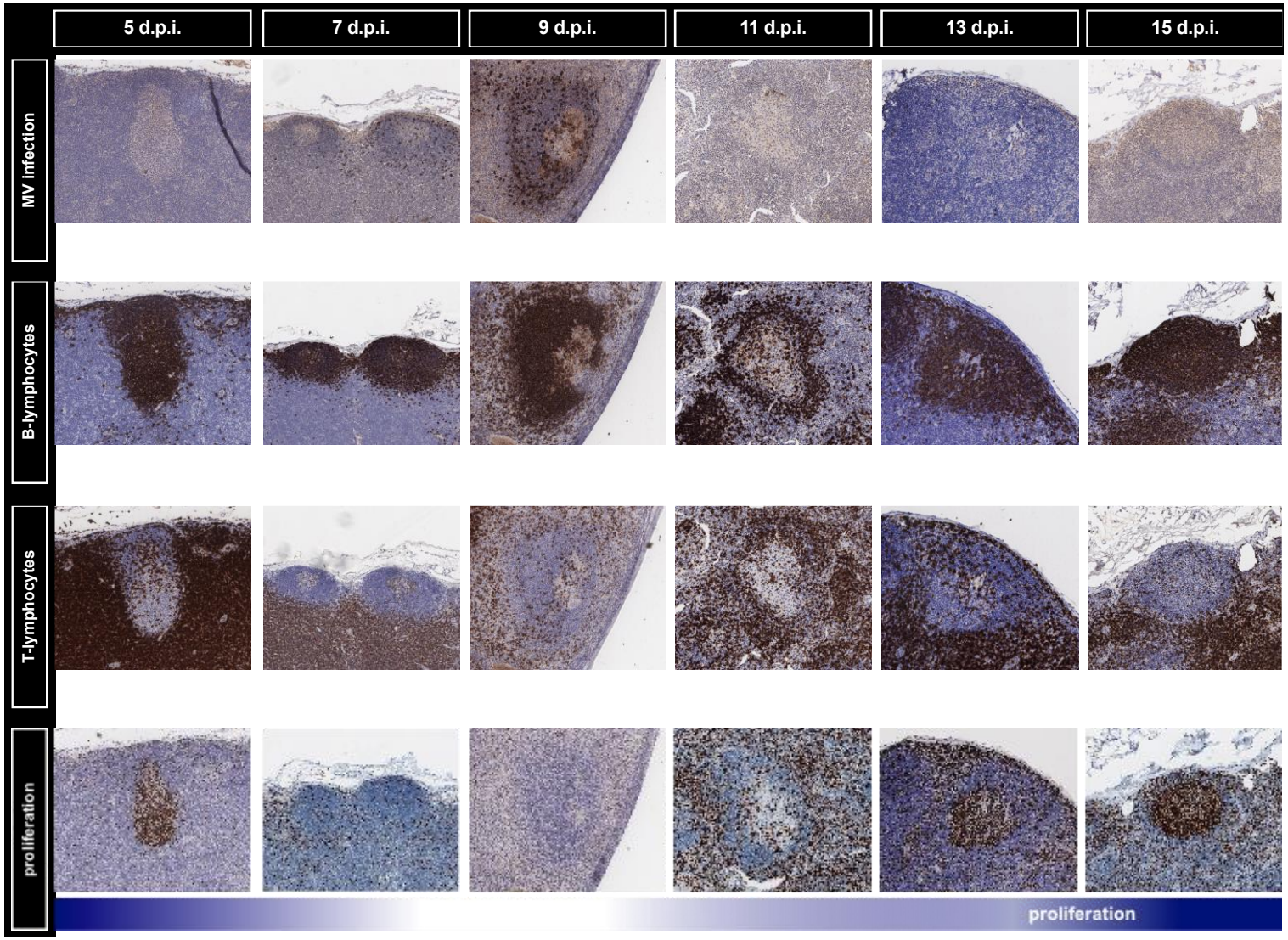
Erasmus MC
University Medical Center Rotterdam

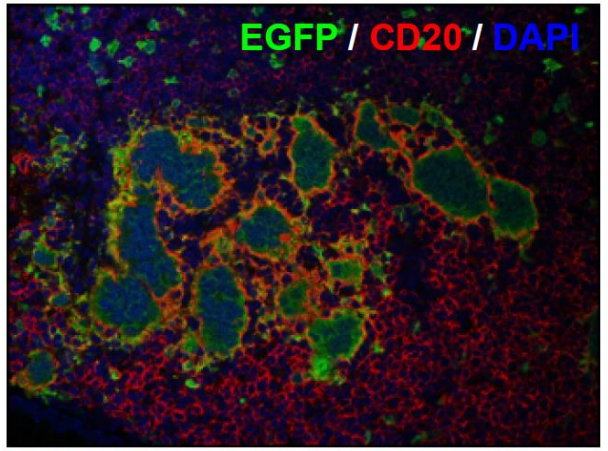
# MV infection of memory T cells *in vivo*

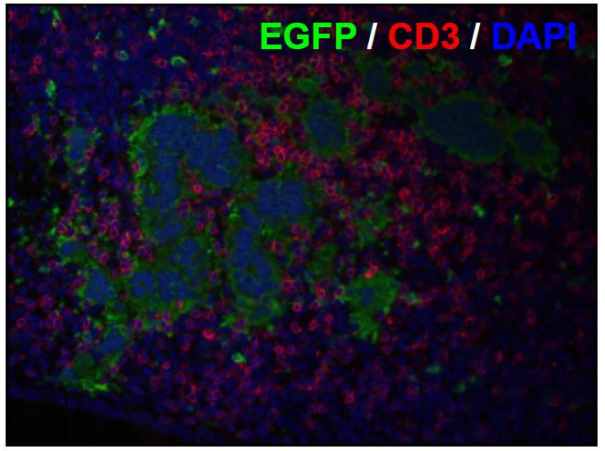



Erasmus MC
University Medical Center Rotterdam

# Lymphocyte depletion in lymphoid tissue



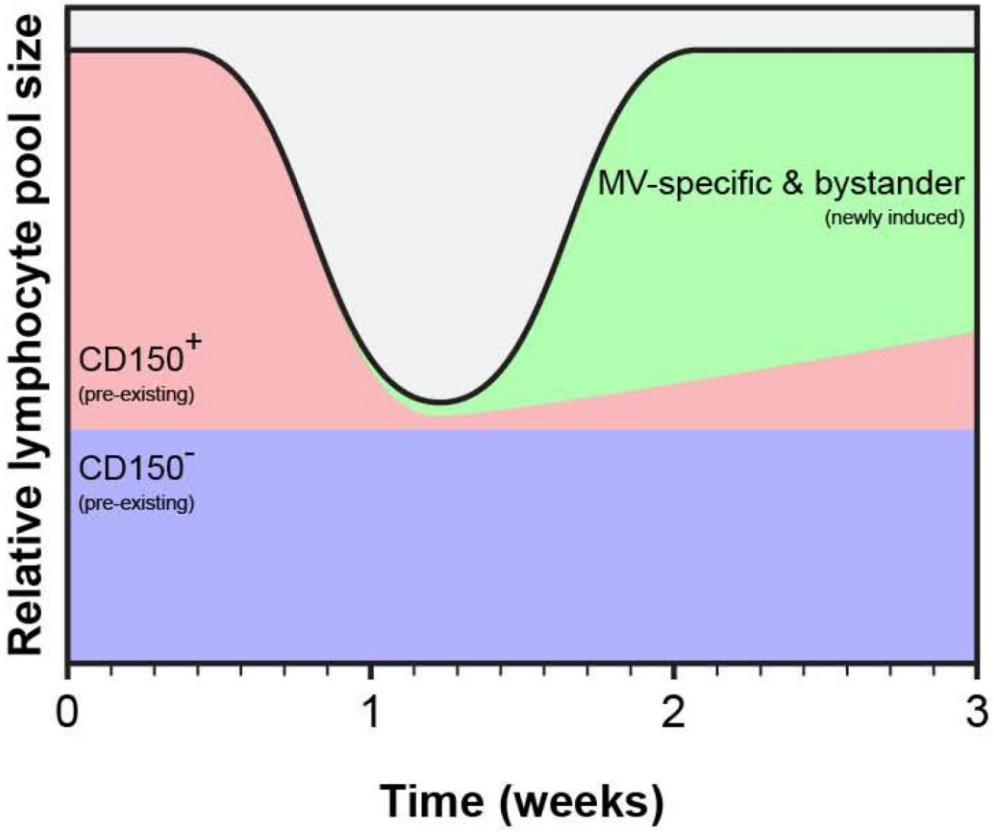




Erasmus MC
University Medical Center Rotterdam

# Immune amnesia model

## How to explain short-duration lymphopenia but long duration immune suppression?




PLoS Pathog 2012, 2014; Science 2015

- Immune suppression: MeV infects and depletes pre-existing CD150$^{+}$ memory cells (shown in red), resulting in **immune amnesia**
- Immune activation: MeV induces a strong MV-specific immune response, resulting in expansion of new lymphocytes (shown in green) which **mask depletion** of pre-existing cells
- New immune cells are effective against measles, but cannot fight common infectious diseases

Erasmus MC
University Medical Center Rotterdam

# Duration of measles immune suppression

Higher incidence rates of GP consultations after measles

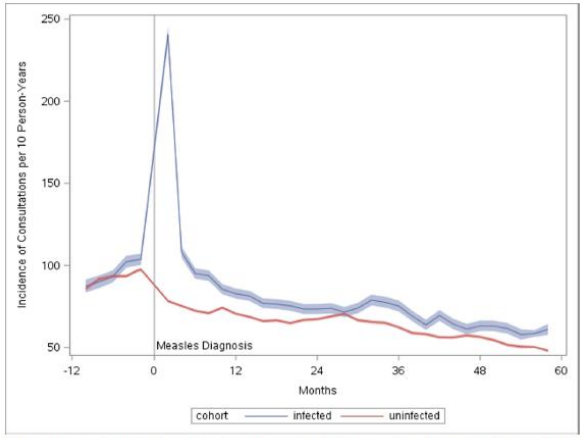



Figure 2 Consultations in measles patients and matched controls. Incidence rates of consultations in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

Higher incidence rates of infections after measles

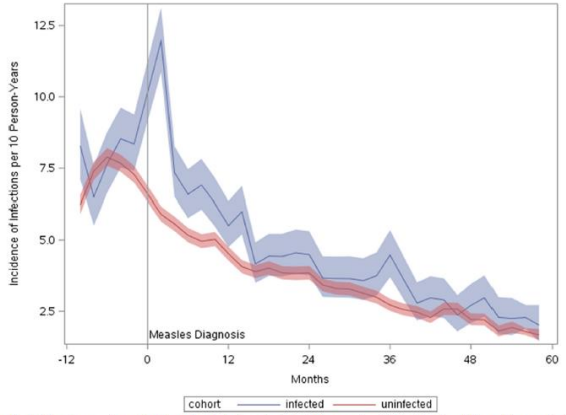



Figure 3 | Infections in measles patients and matched controls. Incidence rates of infections in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

Higher incidence rates of antibiotic prescription incidence rates after measles

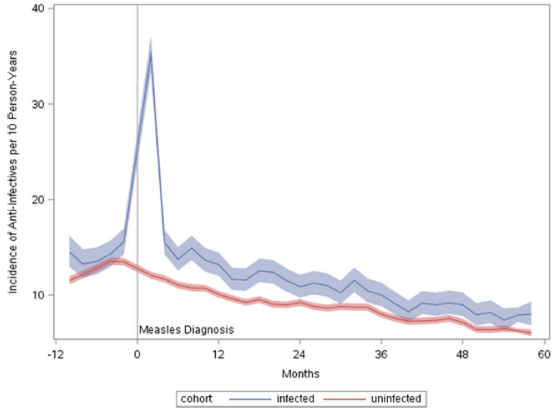


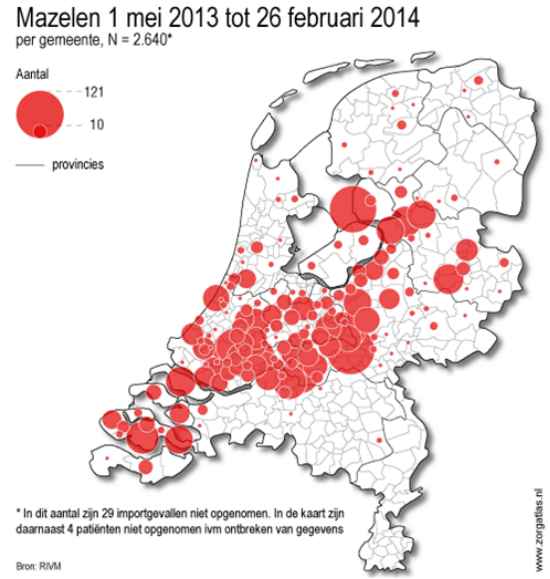

Figure 4 | Anti-infective prescriptions in measles patients and matched controls. Incidence rates of anti-infective prescriptions in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

**Conclusion** Following measles, children had increased rates of diagnosed infections, requiring increased prescribing of antimicrobial therapies. This population-based matched cohort study supports the hypothesis that measles has a prolonged impact on host resistance to non-measles infectious diseases.

Gadroen K, *et al. BMJ Open* 2018;**8**:e021465. doi:10.1136/bmjopen-2017-021465

Erasmus MC
University Medical Center Rotterdam

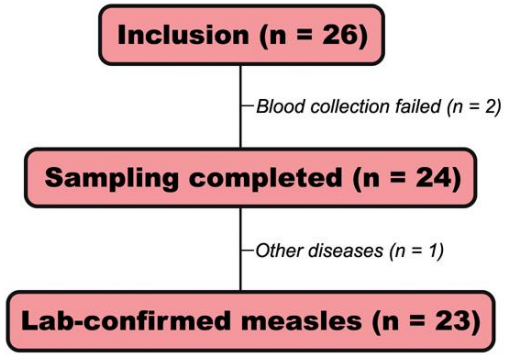
# Clinical study in unvaccinated children

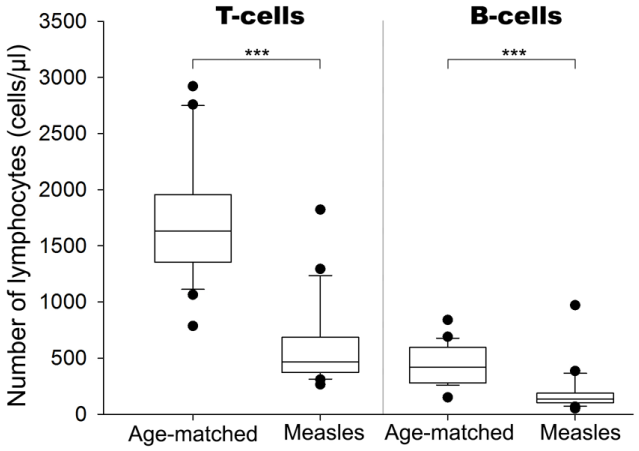


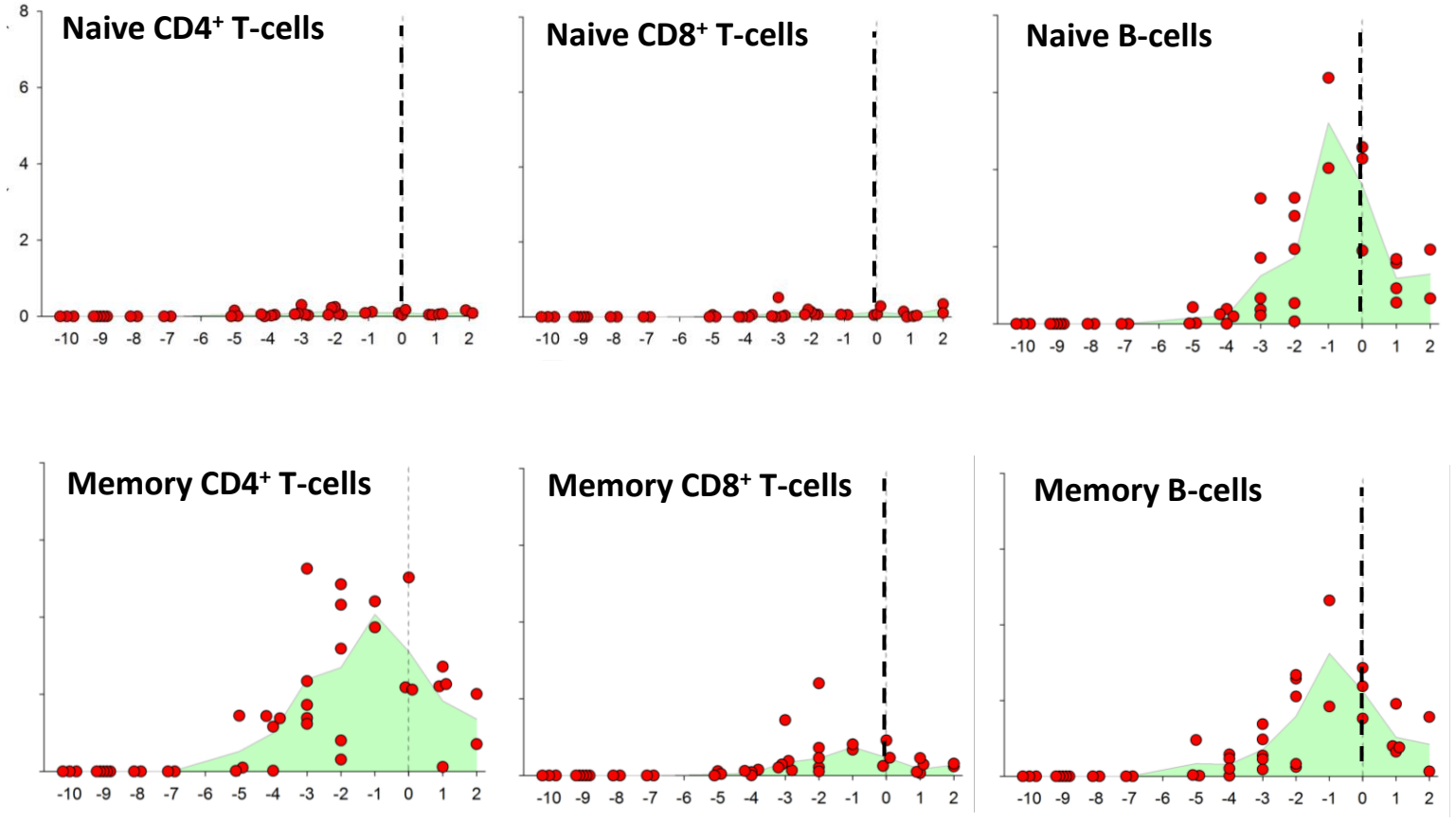

- **Title:** Studies into the mechanism of measles-associated immune suppression during an outbreak of measles in The Netherlands (NL45323.078.13)
- **Objective:** Validate immune suppression model in measles patients
- **Study design:** Observational cohort study
- **Study population:** Unvaccinated children in families, 4-17 years of age

Erasmus MC
University Medical Center Rotterdam

# Cohort A: early acute measles

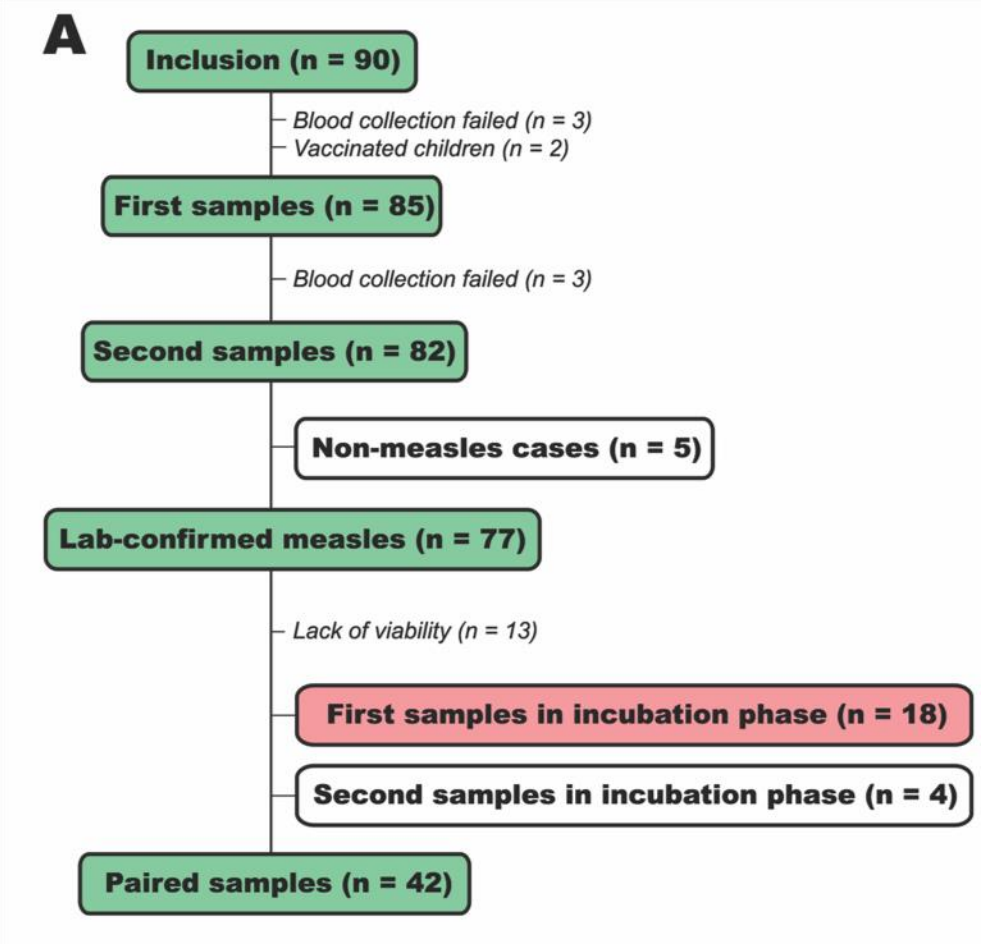


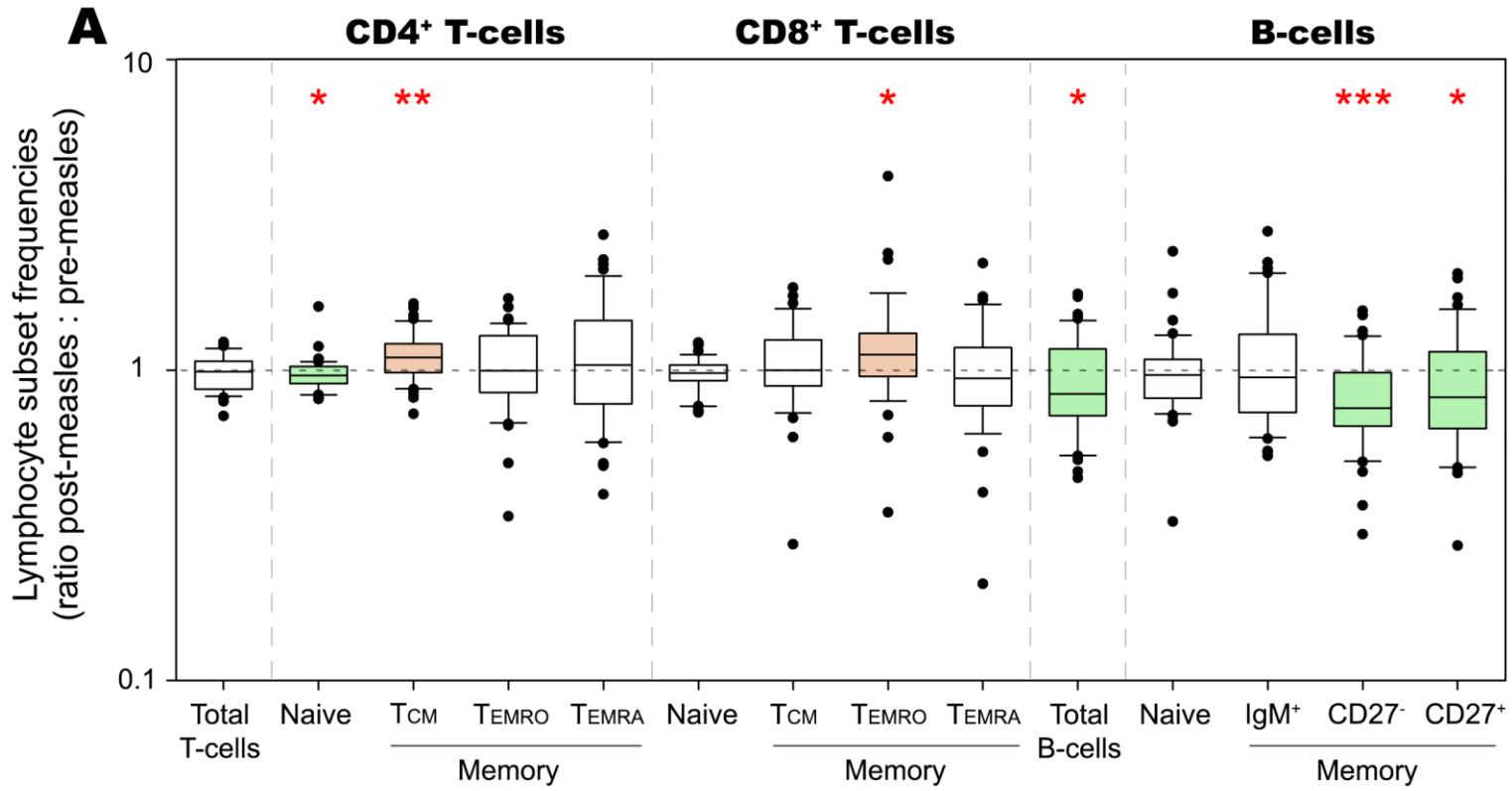




Erasmus MC
University Medical Center Rotterdam

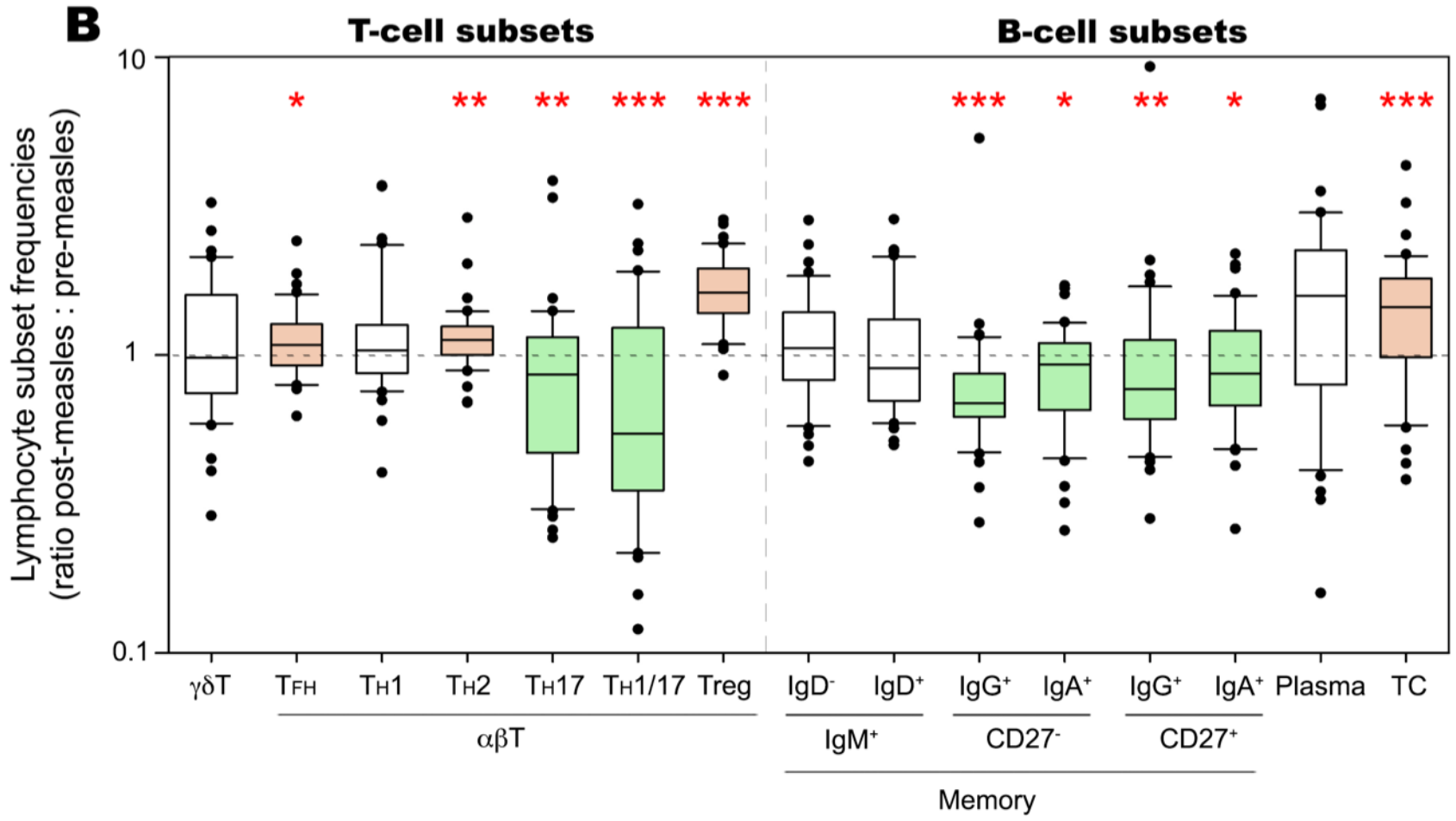
# Cohort B: paired PBMC



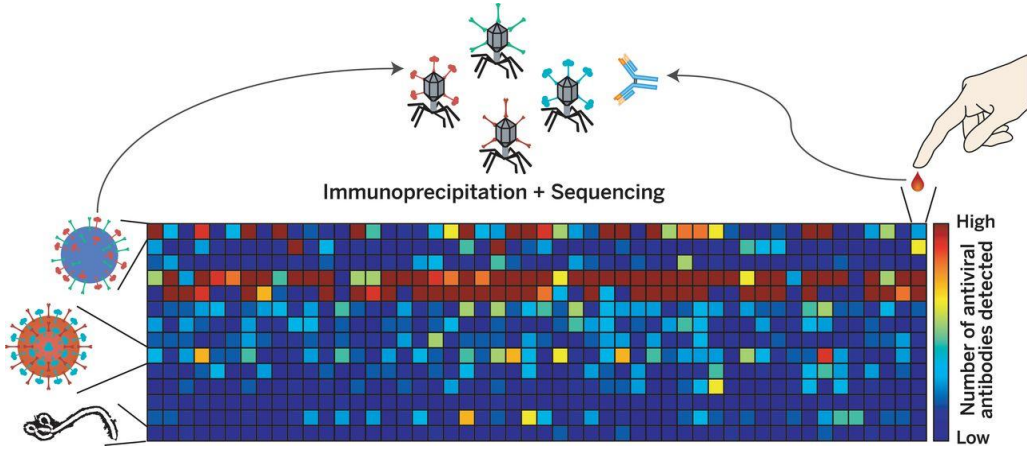

Erasmus MC
University Medical Center Rotterdam

# Cohort B: paired PBMC

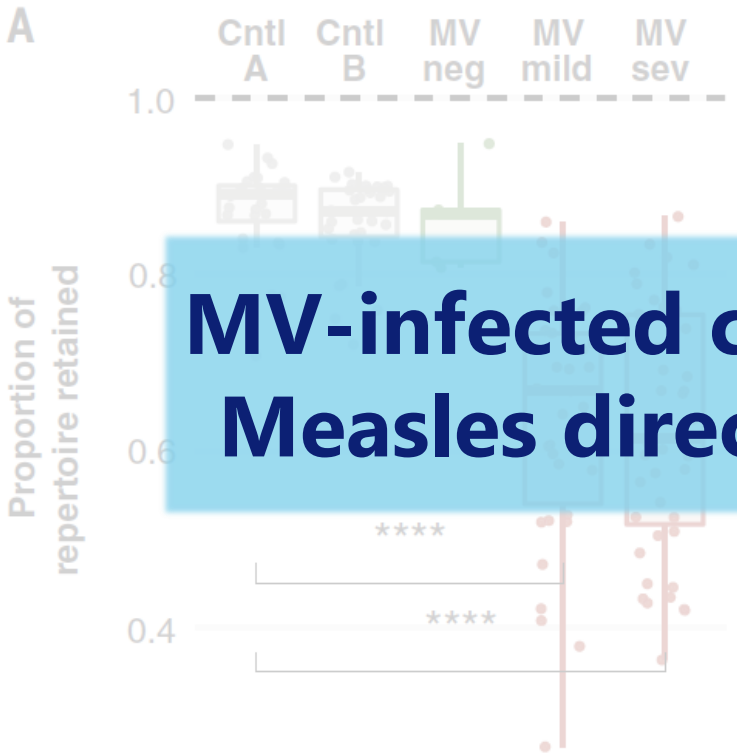


# Effect on antibody repertoire

- **Systematic viral epitope scanning (VirScan)**
  - Comprehensive analysis of antibodies in human sera
  - Bacteriophage display to create a uniform, synthetic representation of peptide epitopes comprising the entire human virome
  - High-throughput DNA sequencing reveal peptides recognized y antibodies
  - Antibodies to short contiguous epitopes (not comformational)



# Effect on antibody repertoire

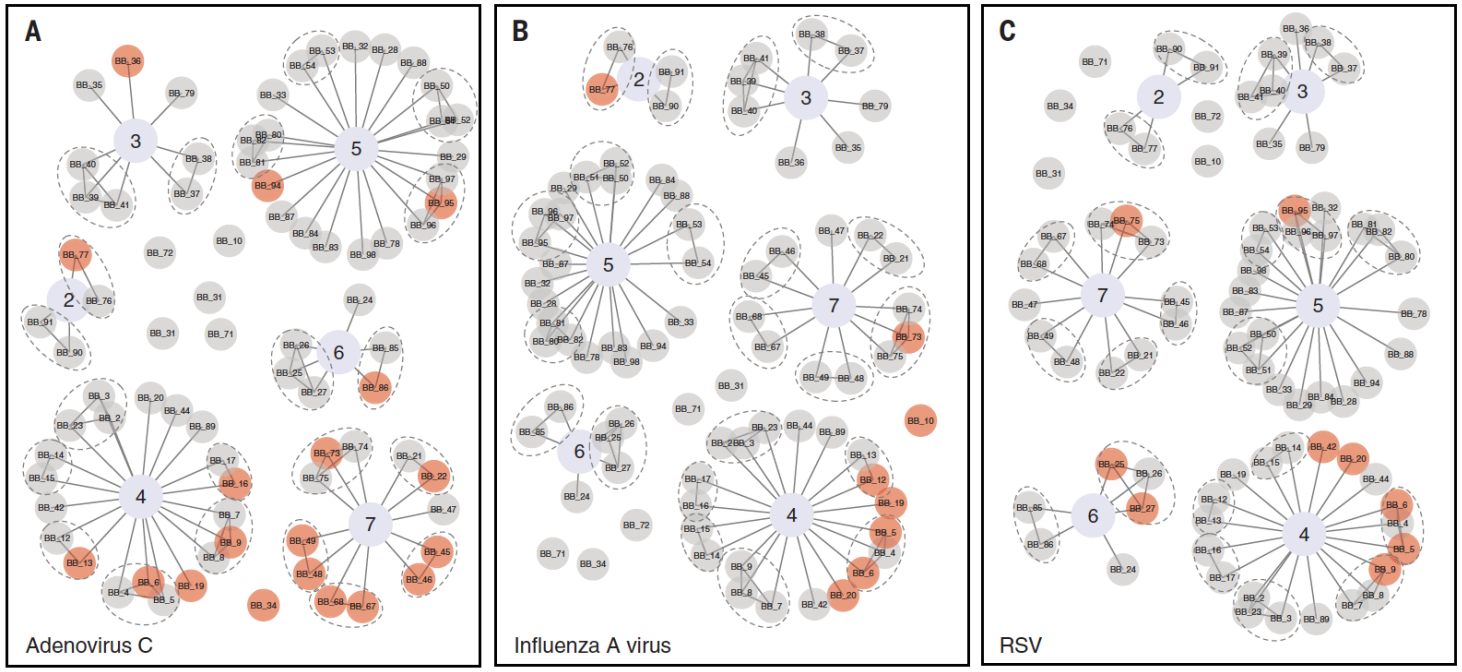



**MV-infected children lose 40% of their ab repertoire**
**Measles directly affects the long-lived plasma cells**

Erasmus MC
University Medical Center Rotterdam

# Effect on antibody repertoire

- **Subset of children had increased hits for particular pathogens**




- Clustering of restoration by postal code / school / household
- Reconstruction of immune memory on a per pathogen basis
- Only respiratory viruses clustered spatially

Erasmus MC
University Medical Center Rotterdam

# Conclusions (4)

- MV preferentially infects **memory cells**
- MV decimates **lymphoid organs**
- **Lymphocyte subsets are preferentially depleted** after measles
- **Antibody repertoire is significantly reduced** after measles

Erasmus MC
University Medical Center Rotterdam

# Acknowledgements


**Erasmus MC department Viroscience**

Brigitta Laksono

Joyce Verburgh

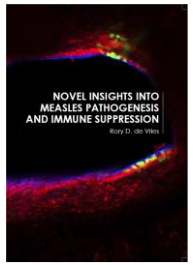
Albert Osterhaus

David van de Vijver

Marion Koopmans

**Rik de Swart**

lembaga pengelola dana pendidikan




**Erasmus MC department Pediatrics**

Eline Visser

Pieter Fraaij

Annemarie van Rossum

**Erasmus MC department Immunology**

Diana van den Heuvel

Menno van Zelm

**Erasmus MC department of General Practice**

Arthur Bohnen

**Erasmus MC department of Medical Informatics**

Kartini Gadroen

Caitlin Dodd

Mirjam Sturkenboom

**RIVM Bilthoven / GGD Gelderland Zuid**

Helma Ruijs

ZonMw

MRC Medical Research Council

COOPERATION

**Princeton University**

Bryan Grenfell

**Harvard University**

Michael Mina

Stephen Elledge

**Sanger Institute**

Velislava Petrova

Paul Kellam

Colin Russell

**University of Pittsburgh**

Paul Duprex