Immune amnesia following infections with measles virus

perspective from a measles outbreak in the Netherlands

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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.

  ![Comparison of reproduction numbers, or $R^0$, for several viruses. $R^0$ is a measure of contagiousness.]

  - Hepatitis C (2)
  - Ebola (2)
  - HIV (4)
  - SARS (4)
  - Mumps (10)
  - Measles (18)
Measles: the disease

- **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)
Cellular receptors for measles 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

**MV is a Lymphotrophic, Myelotrophic and Epitheliotropic virus**
**MV-GFP viruses and animal models**

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

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

*El Mubarak et al., J Gen Virol 2007*
Study objective (II): how is MV disseminated throughout the host?
Dissemination via lymphoid / myeloid cells

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

During peak virus replication MeV mainly targets lymphoid tissues

Massive MeV replication in submucosal tissues
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?
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 \( \text{PBMC < lymphoid tissues < subpopulations in lymphoid tissues} \)

**Hypothesis:** infection and subsequent depletion of memory lymphocytes can explain measles immune suppression and increased susceptibility to opportunistic infections
MV infection of memory T cells in vivo
Lymphocyte depletion in lymphoid tissue

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**B-lymphocytes**

**T-lymphocytes**

**Proliferation**

**MV infection**

**EGFP / CD20 / DAPI**

**EGFP / CD3 / DAPI**
Immune amnesia model

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

- **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.

Duration of measles immune suppression

Higher incidence rates of GP consultations after measles

Higher incidence rates of infections after measles

Higher incidence rates of antibiotic prescription incidence rates after measles

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.

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
Cohort A: early acute measles

Inclusion (n = 26)
- Blood collection failed (n = 2)
Sampling completed (n = 24)
- Other diseases (n = 1)
Lab-confirmed measles (n = 23)

**Naive CD4+ T-cells**

**Naive CD8+ T-cells**

**Naive B-cells**

**Memory CD4+ T-cells**

**Memory CD8+ T-cells**

**Memory B-cells**

Days relative to onset of rash
Cohort B: paired PBMC

A

- Inclusion (n = 90)
  - Blood collection failed (n = 3)
  - Vaccinated children (n = 2)

- First samples (n = 85)
  - Blood collection failed (n = 3)

- Second samples (n = 82)
  - Non-measles cases (n = 5)
  - Lab-confirmed measles (n = 77)
    - Lack of viability (n = 13)
    - First samples in incubation phase (n = 18)
    - Second samples in incubation phase (n = 4)
  - Paired samples (n = 42)

Lymphocyte subset frequencies (ratio post-measles : pre-measles)
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 by antibodies
  - Antibodies to short contiguous epitopes (not conformational)
MV-infected children lose 40% of their ab repertoire
Measles directly affects the long-lived plasma cells
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
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
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