Public Health Ontario | Santé publique Ontario

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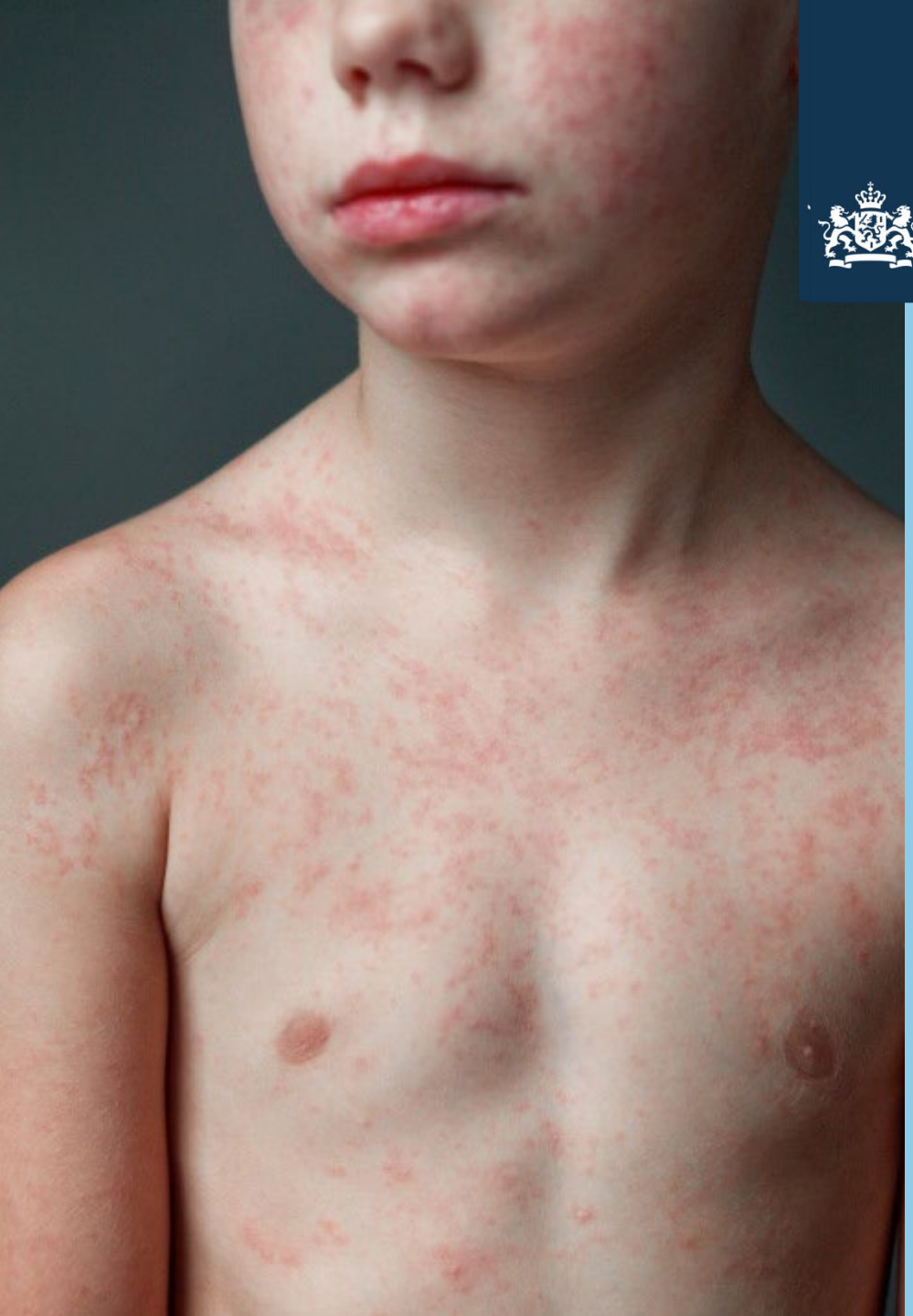
https://youtu.be/ZkSL6Kh-MNk

Please scroll down this file to view a copy of the slides from the session.



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Two decades of measles & rubella outbreaks in the Netherlands

Opportunities to study vaccines, infections and immunity & options for control

Dr. Susan Hahné
RIVM - Centre for Infectious Disease Control Netherlands

Public Health Ontario rounds
14 October 2025

Disclosure Susan Hahné

(potential) conflicts of interest	None
Any commercial interests potentially relevant for this meeting	Co-authored a book: '*Vaccination Programmes: Epidemiology, Monitoring, Evaluation*' Routledge / Open access available Editor-in-Chief *Epidemiology & Infection* Cambridge University Press

Professional background

- Training in health sciences and medicine
- Two years clinical work in internal medicine
- EPIET fellowship (European Programme Intervention Epidemiology Training): Wales, United Kingdom
- Specialisation in public health: UK Faculty of Public Health, London, United Kingdom
- Netherlands: National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
  - PhD on hepatitis B (2012)
  - Head of Department for early warning & surveillance
  - Currently:
    - Senior epidemiologist in vaccine unit
    - Editor-in-Chief *Epidemiology & Infection*

Overview

1. Background
   - Measles and rubella vaccination programmes in the Netherlands
   - Surveillance and monitoring
   - Vaccine coverage: Low coverage subgroups
2. Epidemiology of measles and rubella in the Netherlands
   - Outbreaks
3. Main areas of research at RIVM
4. Interventions to increase uptake of vaccination
5. Synthesis

Learning objectives

1. Identify the risks of measles and rubella in clustered communities with low vaccine coverage.
2. Describe current approaches to measles outbreak control in the Netherlands.
3. Describe current approaches to rubella prevention in the Netherlands.

BACKGROUND

The Netherlands

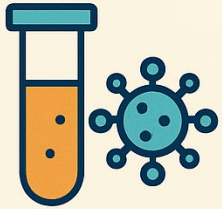
- 18 million inhabitants
- Capital: Amsterdam. Government residence: The Hague
- 2025: 80 years freedom celebrations
- School system
  - Dutch constitution article 23: Freedom of education
  - State funded schools of various denominations
    - General (37%), Catholic (30%), Protestant (27%)
    - Orthodox protestant (3%), Islamic (1%), Anthroposophical (1%)
- Public health
  - Government Ministry of Health and Welfare
  - National Public Health Institute (RIVM)
  - Regional Public Health Institutes (GGDs)
  - Health Council
  - National Outbreak Management Team
  - International: ECDC & WHO Euro

Measles & rubella vaccination the Netherlands

- 1974 Monovalent rubella vaccination for girls at age 11 years
- 1976 Monovalent measles vaccination at age 14 months
- 1987 MMR at age 14 months and 9 years
- 2024 2nd MMR at age 3 years

- Organisation of vaccine delivery
  - National vaccine register linked to population register (Praeventis)
    - Used for call and recall and monitoring
  - Vaccines delivered in well-baby clinics health checks and advice

COMPONENTS OF VPD SURVEILLANCE



SERO-SURVEILLANCE

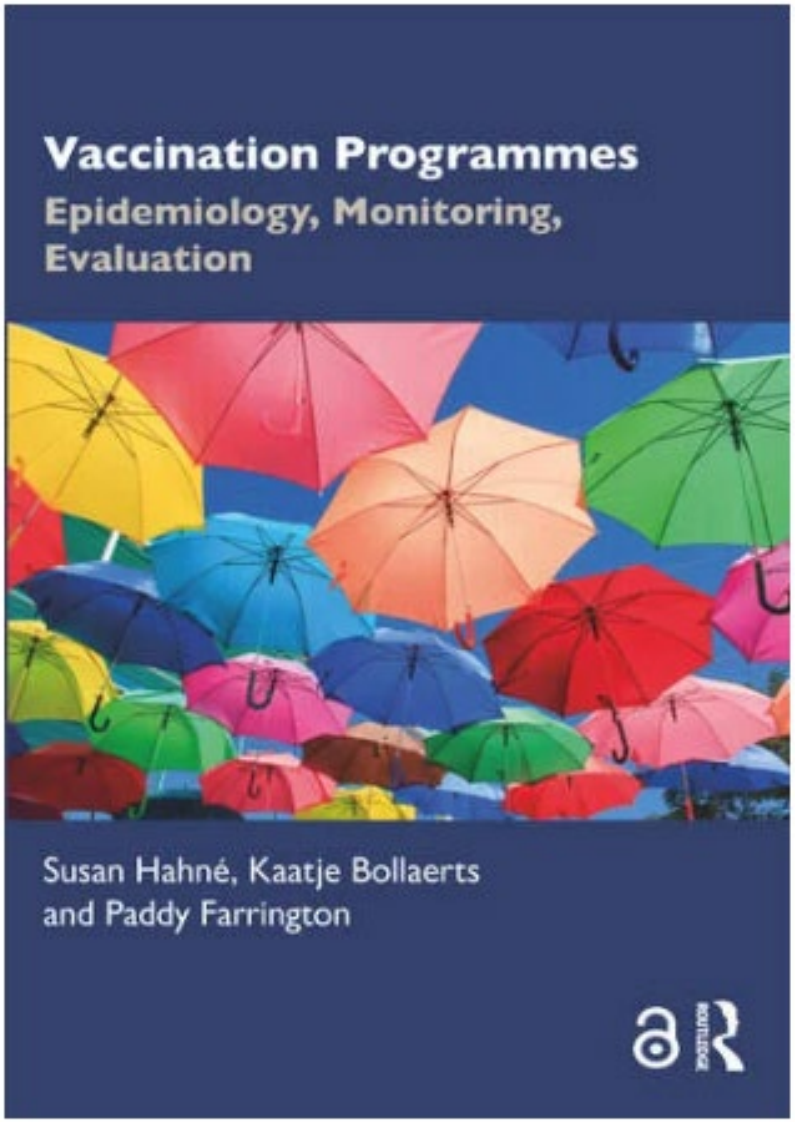
DISEASE SURVEILLANCE

PATHOGEN SURVEILLANCE

ADVERSE EVENTS

VACCINE COVERAGE

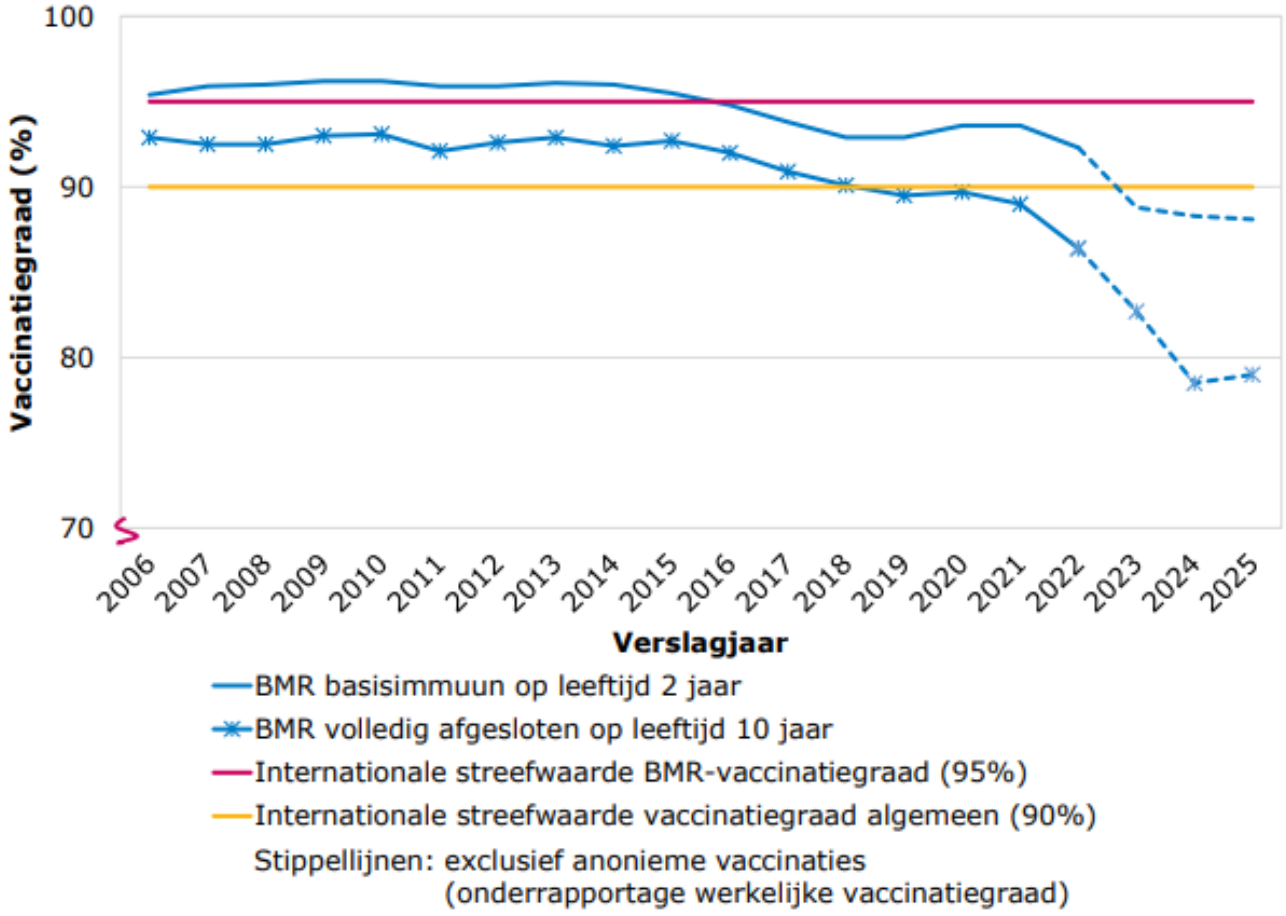
ATTITUDES TOWARDS VACCINATION



PDF available online free of charge

MMR vaccine coverage

1st and 2nd dose, The Netherlands, 2006-2025



Source: Annual Vaccine Coverage Report RIVM, 2025

EUROPE

Report of the 22nd Meeting of the European Regional Certification Commission for Poliomyelitis Eradication

Copenhagen, Denmark, 21-22 June 2009

‘Bible-belt’

- Orthodox Protestant Christians: Reformed congregations
  - established around 1520
  - refusal of vaccination since 18th century (smallpox)
  - religious arguments of predestination and divine providence
  - ≈ 250.000 people (1.5% Dutch population)
  - vaccine coverage ≈ 60%
- Socio-geographic clustering
  - ‘Bible-belt’
  - orthodox reformed schools
  - less benefit from herd-protection
- Represented in the Dutch Parliament
  - SGP (Reformed Political Party)

Heidelberg catechism (1563) about Divine providence

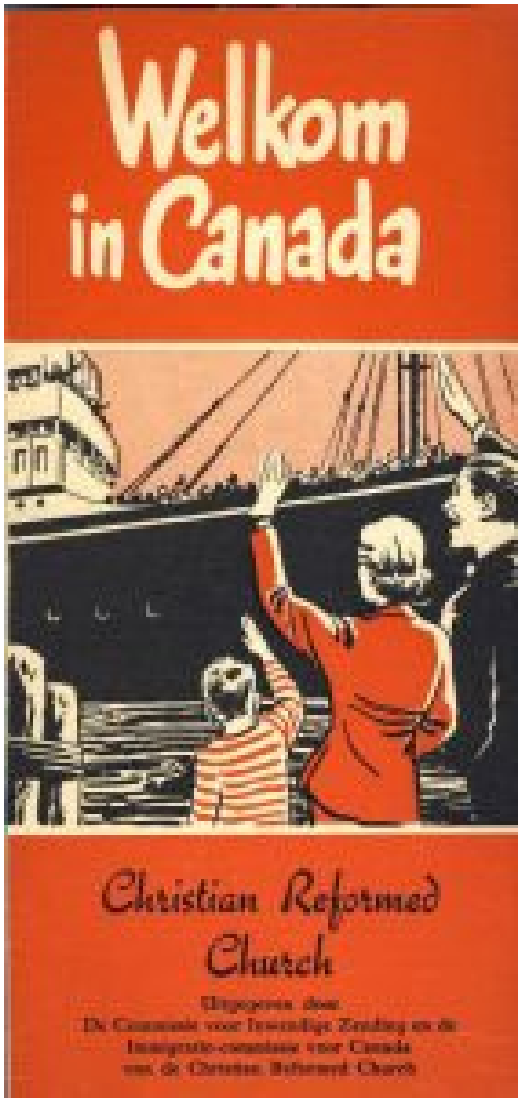
Question 27: What dost thou mean by the providence of God?

The almighty and everywhere present power of God; whereby, as it were by his hand, **he upholds and governs** heaven, earth, and all creatures; so that herbs and grass, rain and drought, fruitful and barren years, meat and drink, **health and sickness**, riches and poverty, yea, and **all things come, not by chance, but be his fatherly hand.**

Source: Refo500

Migration of orthodox protestant Christians from Netherlands to Canada

- Mainly in 1950s, after WWII
- 185.000 Dutch migrants to Canada
  - 66% Reformed



https://origins.calvin.edu/2020/09/08/when-canada-was-a-crc-mission-field/

Polio & MMR outbreaks The Netherlands, Canada and the US

Year	Disease	Approximate number of cases	Population	Spread
1978	Polio	100	Orthodox Reformed	Canada & US
1992-'93	Polio	100	Orthodox Reformed	Canada
1999-'00	Measles	3,300	Orthodox Reformed	Canada
2004-'05	Rubella	400	Orthodox Reformed	Canada
2005-'09	Mumps	not known	Orthodox Reformed	Canada
2008	Measles	100	Anthroposophic	Not reported
2013-'14	Measles	2,600	Orthodox Reformed	Canada & US

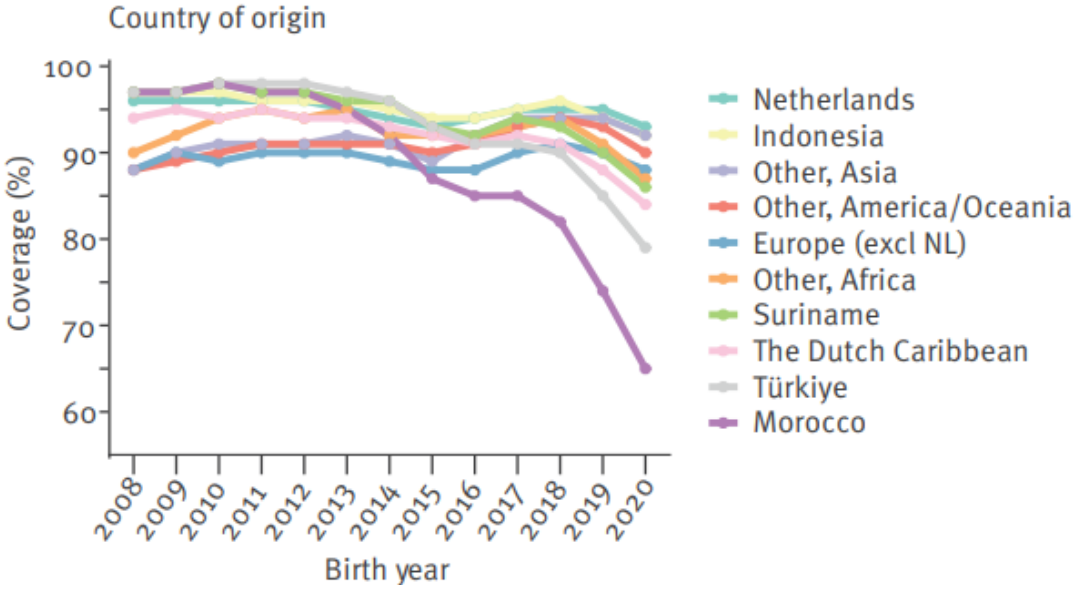
‘ I beg you:
Do NOT do this to
your children’

Other low vaccine coverage subgroups

- PhD Joyce Pijpers (2022-2026)
- Methods
  - National vaccine register linked to socio-demographic data at individual level in secure environment of Statistics Netherlands
  - Birth cohort 2008-2020; MMR-1 and DTP
  - Multivariable Poisson regression to assess independent associations and changes over time
- Results
  - Childhood vaccination coverage has decreased in all population groups in the Netherlands
  - Faster decline in Dutch children of non-Dutch origin, children not attending daycare, children of larger families, children of self-employed mothers and those from lower income households
  - Multi-variable analysis: children of non-Dutch origin, particularly Moroccan and Turkish, showed more pronounced declines (respectively −25% and −12%) than children of Dutch origin in cohort 2020

Source: Pijpers, *Eurosurveillance* October 2025

Decline in MMR coverage over time by country of origin



Source: Pijpers, October *Eurosurveillance* 2025

Vaccine coverage at primary school level

Birth cohorts 2013-2022, as of October 2024

Denomination	MMR-1	DTP
Catholic	96%	95%
Protestant	95%	95%
General	94%	94%
Orthodox protestant	57%	58%
Islamic	74%	75%
Anthroposophic	78%	77%

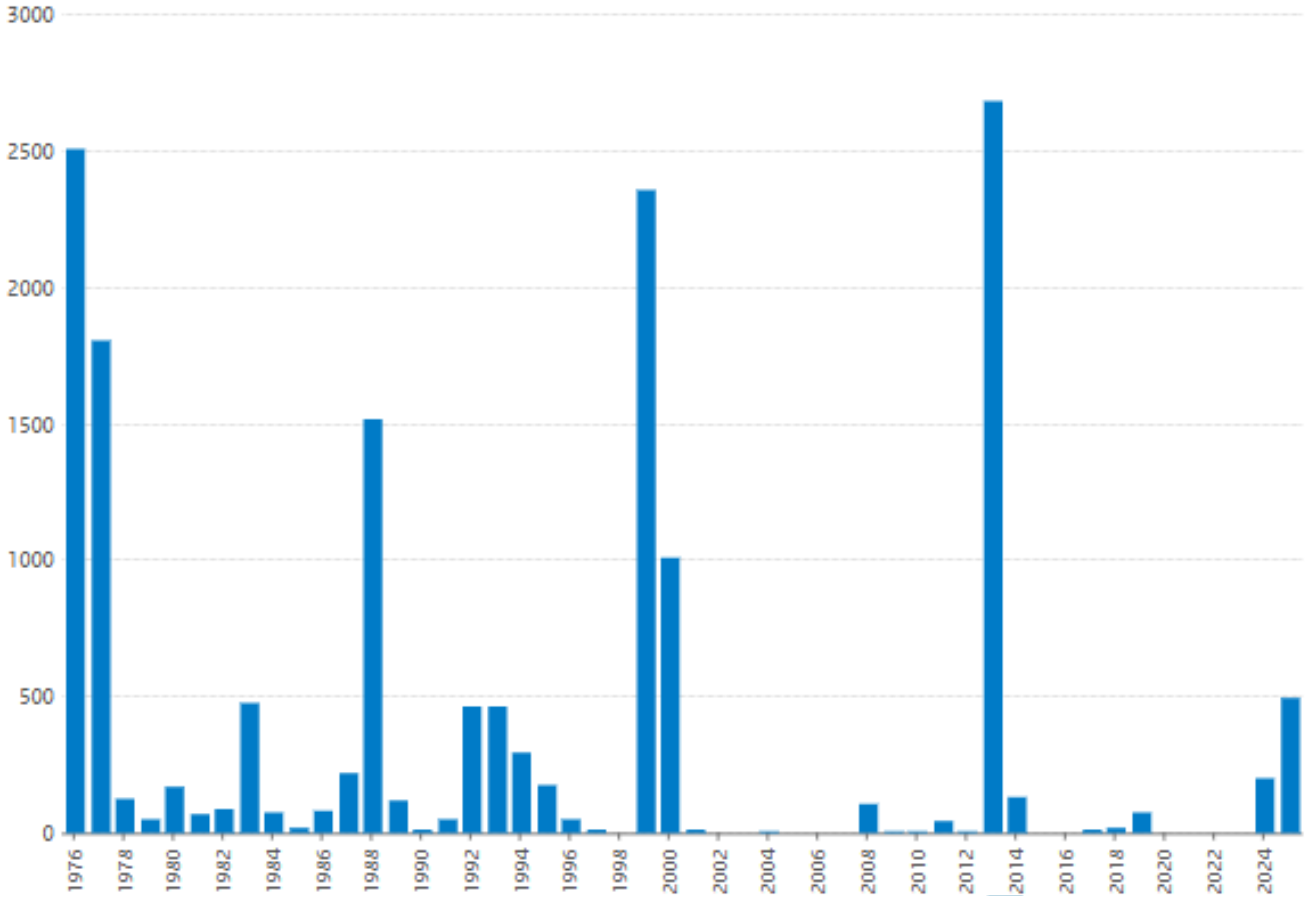
Source: Vaccine coverage report, RIVM, June 2025

Whether and how to communicate these recent findings?

- Risk of stigmatization with adverse effect on equitable vaccine uptake?
- '*Health protection's narrow and unreflective paradigm implies a rather blind eye for the stigmatizing character of its own practices and its role in the persistence of health inequalities*.' K. Horsman *SSM Qualitative Research in Health 2025*
- RIVM: we need a systematic approach
  - to define areas of uncertainly
  - to make sure the rights, interests and preferences of stakeholders are fairly weighed in decision making
- This 'moral deliberation' was carried out in a meeting with about 15 participants
  - Defined methods
- Outcomes
  - One extra main stakeholder meeting was organized
  - Text of reports were improved before made public
- Implications for epidemiologic practice
  - Need to seek better proxies for risks
    - networks of unvaccinated individuals may be a better proxy than individuals' characteristics

EPIDEMIOLOGY OF MEASLES AND RUBELLA IN THE NETHERLANDS

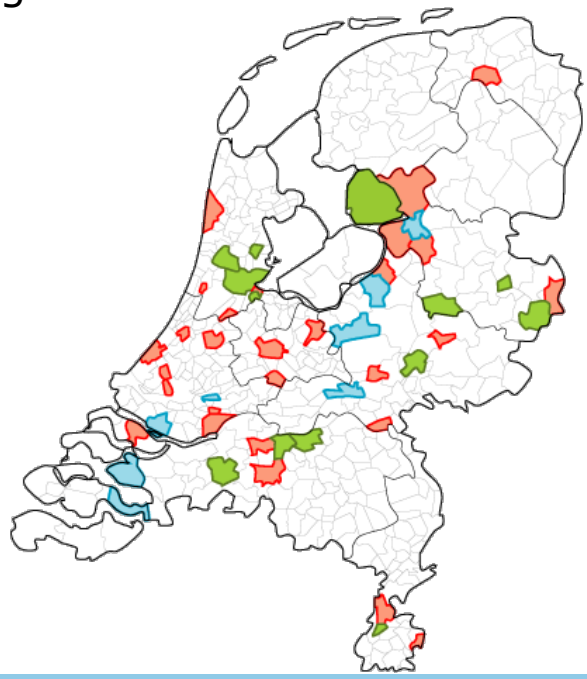
Measles: Reported number of cases per year The Netherlands, 1976-2025*



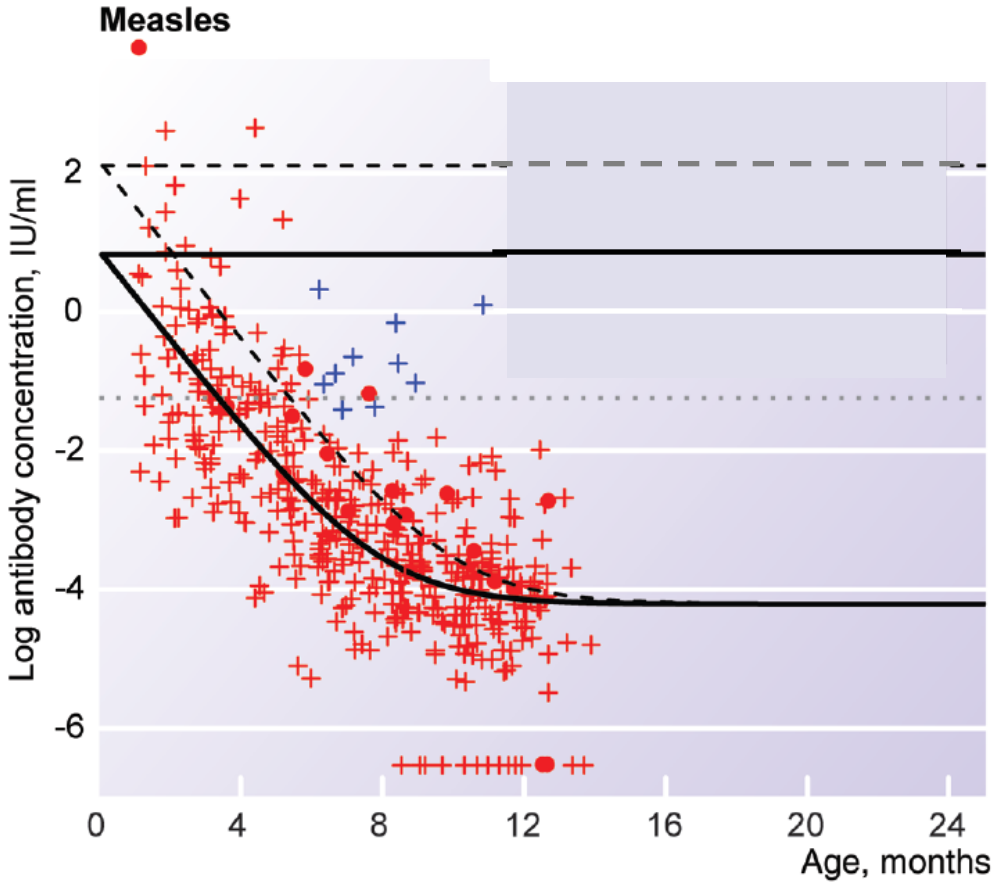
Source: www.rivm.nl * up to 18 June 2025

Risk assessment based on sero-epidemiology

- 'Pienter'-studies (1995/96, 2006/7, 2016/2017)
- Aim: monitor national immunisation programme (NIP)
- ≈ 8,000 participants, population based two stage cluster sample
- Oversampling in low vaccine coverage areas and migrants
- Questionnaire and venous blood sample
- Samples tested for antibodies (immunity/infection)
  - many pathogens, also non-NIP
  - luminex technology



Maternal antibodies



- Bible-belt ------
- \+ General population ——

Susceptibility threshold

Due to vaccination programme: Infants susceptible sooner:
3.3 months instead of 5.3

Waaijenborg et al, JID, 2012

Epidemiol. Infect. (2014), **142**, 1100–1108. © Cambridge University Press 2013
doi:10.1017/S0950268813001532

High risk of a large measles outbreak despite 30 years of measles vaccination in The Netherlands

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National Institute for Public Health and the Environment, Centre for Infectious Disease Control, Bilthoven, The Netherlands

Received 29 January 2013; Final revision 15 May 2013; Accepted 30 May 2013; first published online 6 August 2013

SUMMARY

Our aim was to assess progress towards measles elimination from The Netherlands by studying humoral measles immunity in the Dutch population. A population-based seroepidemiological study was conducted in 2006–2007 ($N=7900$). Serum samples were analysed by a bead-based multiplex immunoassay. IgG levels $\geqslant 0{\cdot}2$ IU/ml were considered protective. The overall seroprevalence in the Dutch population was 96%. However, 51% of socio-geographically clustered orthodox Protestant individuals aged <10 years were susceptible. Infants might be susceptible to measles between ages 4 months and 14 months, the age at which maternal antibodies have disappeared and the first measles, mumps, rubella (MMR) vaccination is administered, respectively. Waning of antibody concentrations was slower after the second MMR vaccination than after the first. The Netherlands is at an imminent risk of a measles outbreak in the orthodox Protestant minority. To prevent subsequent transmission to the general population, efforts to protect susceptible age groups are needed.

Key words: Infectious disease epidemiology, measles (rubeola), MMR vaccination, serology, vaccine preventable diseases.

SURVEILLANCE AND OUTBREAK REPORT

Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology

T Woudenberg [1,2], RS van Binnendijk [1], EAM Sanders [1,2], J Wallinga [1,3], HE de Melker [1], WLM Ruijs [1], SJM Hahné [1]
1. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
2. University Medical Center Utrecht, Utrecht, the Netherlands
3. Leiden University Medical Center, Leiden, the Netherlands

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Citation style for this article:
Woudenberg T, van Binnendijk RS, Sanders EAM, Wallinga J, de Melker HE, Ruijs WLM, Hahné SJM. Large measles epidemic in the Netherlands, May 2013 to March 2014: changing epidemiology. Euro Surveill. 2017;22(3):pii=30443. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2017.22.3.30443

Article submitted on 06 January 2016 / accepted on 21 October 2016 / published on 19 January 2017

Since the early 1990s, the Netherlands has experienced several large measles epidemics, in 1992–94, 1999–2000 and in 2013–14. These outbreaks mainly affected orthodox Protestants, a geographically clustered population with overall lower measles-mumps-rubella first dose (MMR-1) vaccination coverage (60%) than the rest of the country (>95%). In the 2013–14 epidemic described here, which occurred between 27 May 2013 and 12 March 2014, 2,700 cases were reported. Several control measures were implemented including MMR vaccination for 6–14-month-olds and recommendations to reduce the risk in healthcare workers. The vast majority of reported cases were unvaccinated (94%, n=2,539), mostly for religious reasons (84%, n=2,135). The median age in the epidemic was 10 years, 4 years older than in the previous epidemic in 1999–2000. A likely explanation is that the inter-epidemic interval before the 2013–2014 epidemic was longer than the interval before the 1999–2000 epidemic. The size of the unvaccinated orthodox Protestant community is insufficient to allow endemic transmission of measles in the Netherlands. However, large epidemics are expected in the future, which is likely to interfere with measles elimination in the Netherlands and elsewhere.

immunisation programme (NIP) in 1976 for all infants at 14 months of age. Since 1987, a two-dose programme using measles-mumps-rubella (MMR) vaccine has been offered at 14 months and 9 years of age. Vaccine coverage of the first dose of MMR vaccination has been above 95% for 20 years [4]. Coverage for two doses at the age of 10 years has been around 93% for 10 years. Introduction of measles vaccination in the Dutch NIP resulted in a large decrease in the number of reported cases [5]. However, epidemics still occur due to socio-geographically clustered individuals who refrain from vaccination. A large measles epidemic occurred in 1999–2000 with 3,292 reported cases, most of whom were unvaccinated (94%) and belonged to the orthodox Protestant community (83%) [6]. Between 2001 and 2012 the incidence of measles was lower than the five cases per million set as a target by the World Health Organisation (WHO) in 2010 [7], except for 2008 when the incidence was seven per million, due to an outbreak in individuals with anthroposophic beliefs [8].

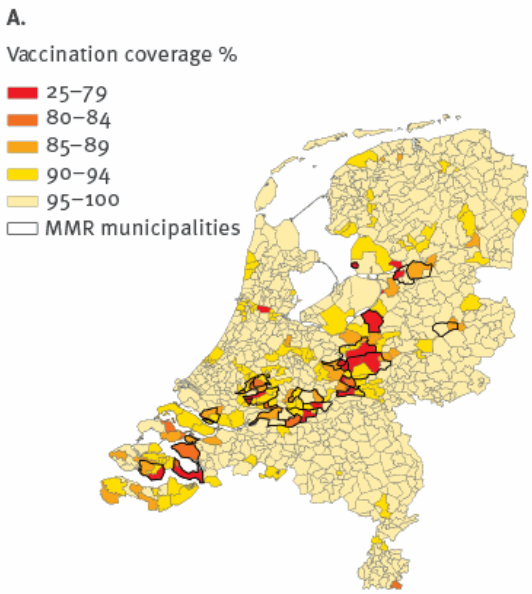
The orthodox Protestant population comprises around 1% of the total population in the Netherlands [9]. Vaccine coverage in these communities is around 60% on average, but varies widely between churches, with coverage ranging from less than 30% among mem-

The 2013/2014 outbreak

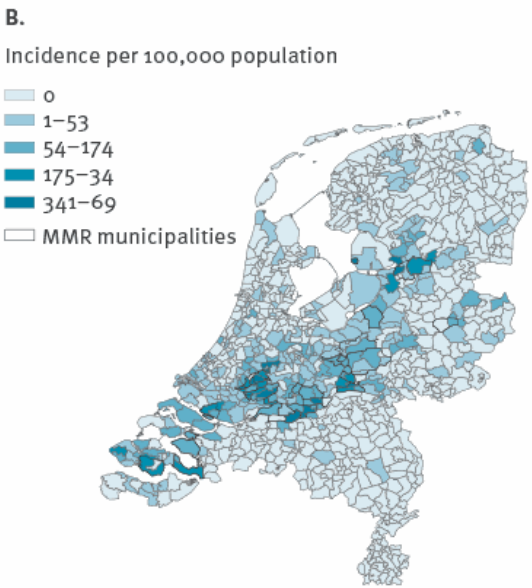
- 2.700 reported cases
- Completeness of reporting: 9%*
- Estimated number of cases: 31.400
  - 94% unvaccinated; 84% based on orthodox religious grounds
  - 7% hospitalized (n=181)
  - 2 fatal cases (encephalitis & pneumonia; SSPE)

Measles outbreak 2013/2014

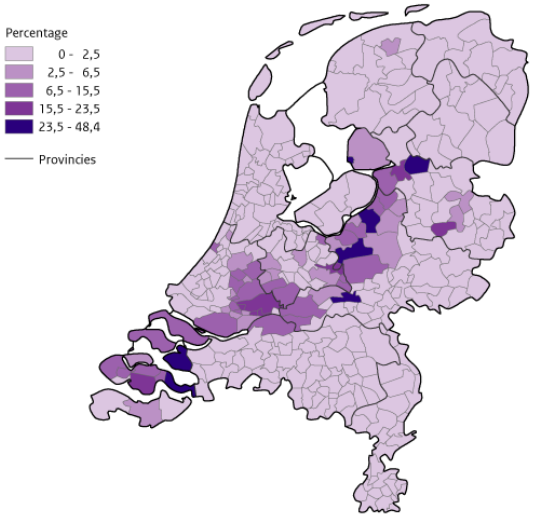
MMR coverage

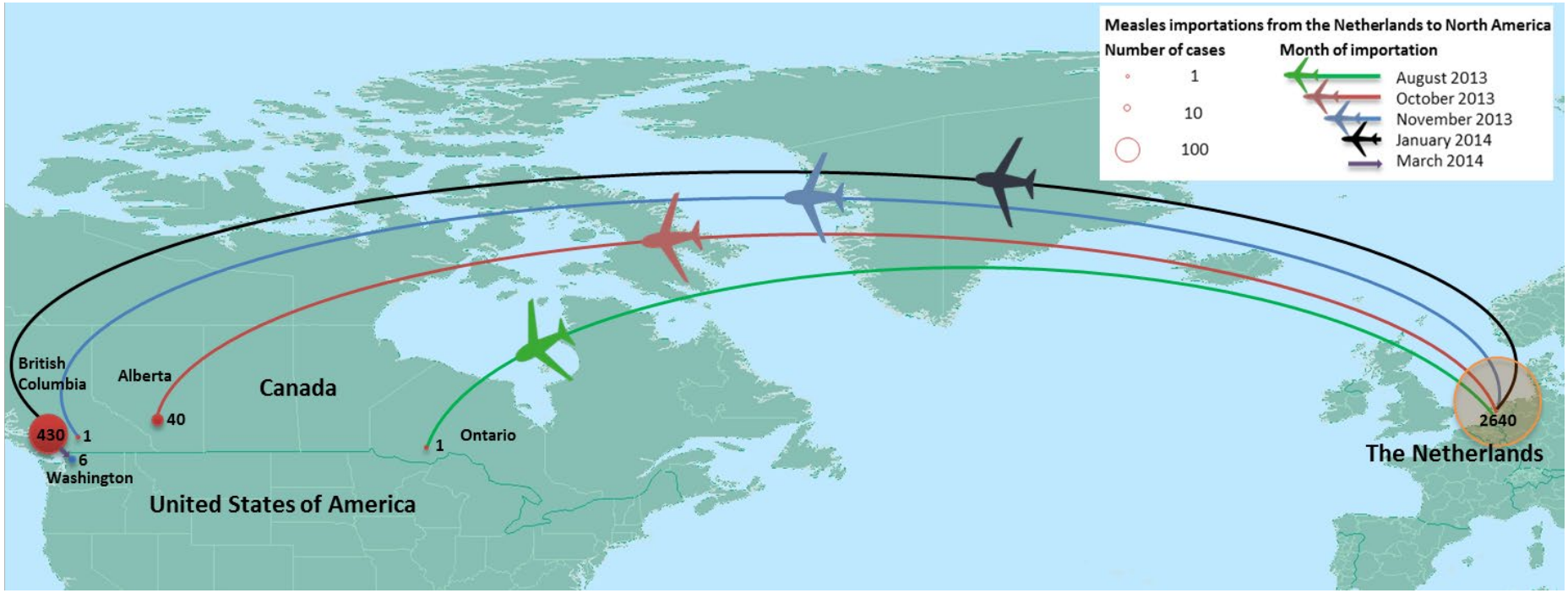


Measles incidence



Votes for State Reformed Party, national government elections 2023





Distribution of measles importations and extent of spread from the Netherlands to Canada and the United States, May 2013 - April 2014

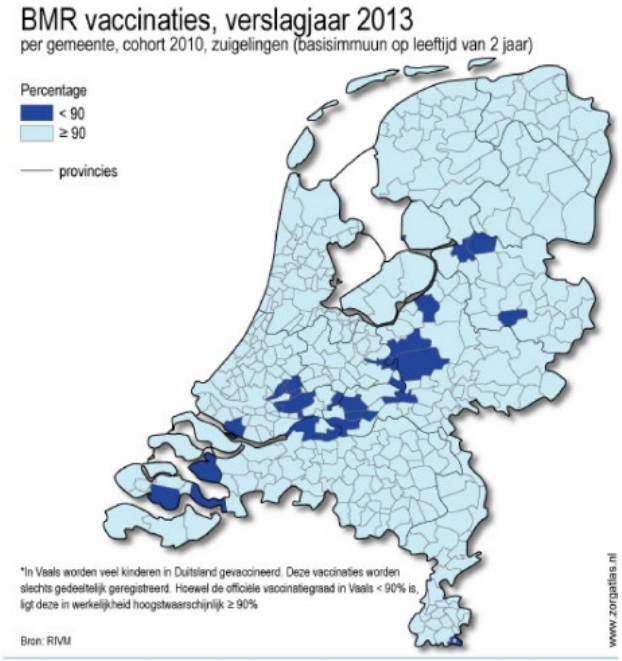
Figure: Laura Nic Lochlainn

British Columbia Experiencing Biggest Measles Outbreak Ever; Spreading to US

Christine Rousselle | Apr 02, 2014

Outbreak control

- Early MMR from 6 months of age in 29 municipalities with coverage <90%
  - balance of risk of infection and of suboptimal effectiveness
- Religious information leaflets



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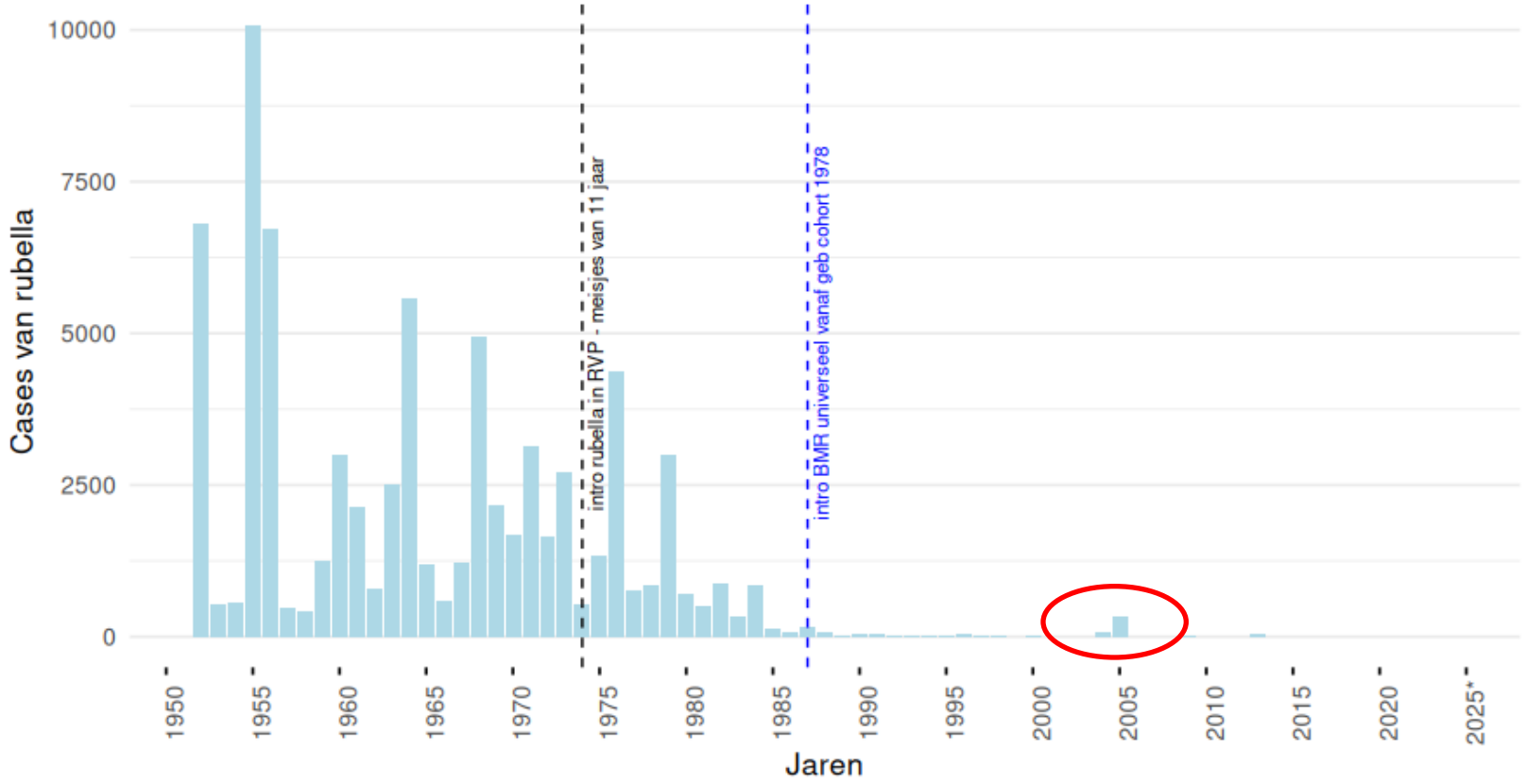
  - 7% hospitalized (n=181)
  - 2 fatal cases (encephalitis & pneumonia; SSPE)

The recent increase in cases

- 2025: 520 cases up to 8 October
  - 8% acquired in Morocco
  - No increase in Bible-Belt
  - 1 fatal case

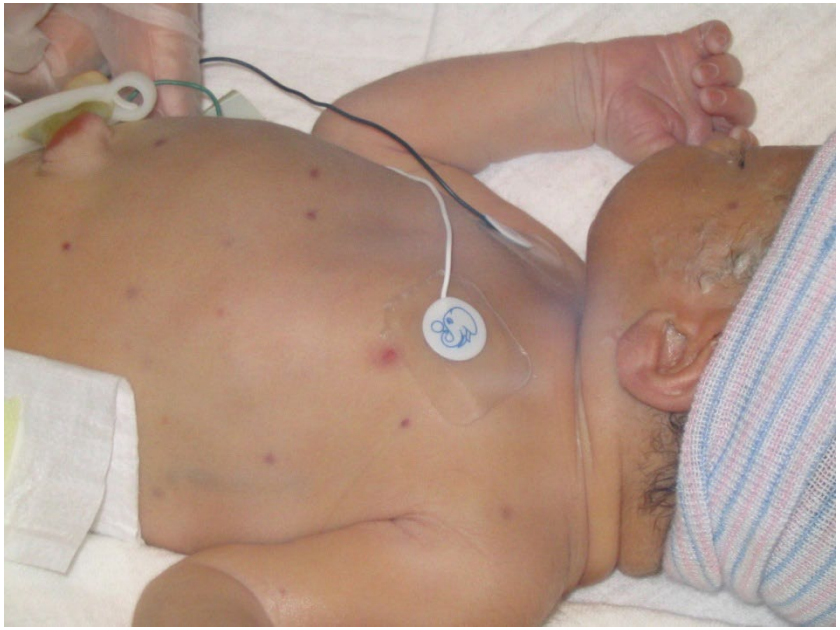
Rubella: Reported number of cases per year The Netherlands, 1950-2025*



Source: www.rivm.nl * up to 13 October 2025

The 2004/2005 outbreak of rubella

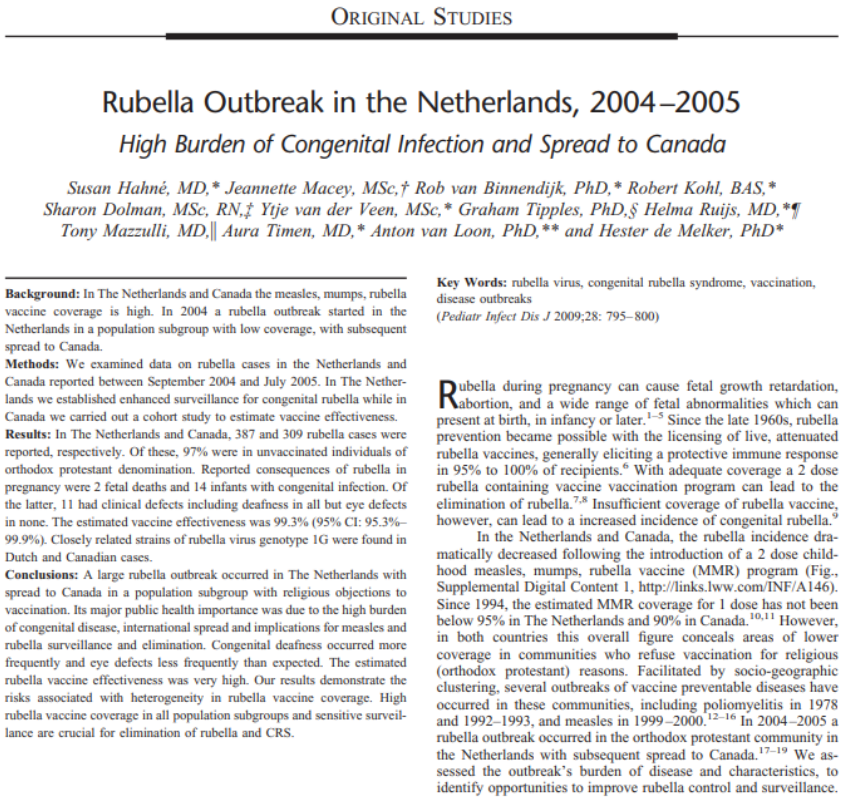
- 387 notified cases
- 2 fetal deaths, 14 infants with congenital infection
  - of these, 11 with defects



- Microcephalic
- Enlarged liver and spleen
- Congenital heart defect
- Bones: 'celery stalk signs'
- Skin: 'blueberry muffin spots'
- Calcifications in brain
- Nearly completely deaf
- Slow psychomotor development
- Increased risk of: diabetes, thyroid disease, growth hormone deficiency, Addison's disease

The 2004/2005 outbreak of rubella - Canada

- 309 cases, all in Ontario
- 99% orthodox protestant community in South-West Ontario
- 10 cases in pregnant women
  - 2 congenital infection
  - no congenital malformations at birth but no f/u info available
- If no rubella virus circulation since in this community, possibly now higher risk of CRS outbreak after introduction of rubella than in 2004/2005



ORIGINAL STUDIES

Rubella Outbreak in the Netherlands, 2004–2005

High Burden of Congenital Infection and Spread to Canada

Susan Hahné, MD, Jeannette Macey, MSc,† Rob van Binnendijk, PhD,* Robert Kohl, BAS,* Sharon Dolman, MSc, RN,‡ Ytje van der Veen, MSc,* Graham Tipples, PhD,§ Helma Ruijs, MD,*¶ Tony Mazzulli, MD,‖ Aura Timen, MD,* Anton van Loon, PhD,** and Hester de Melker, PhD**

Background: In The Netherlands and Canada the measles, mumps, rubella vaccine coverage is high. In 2004 a rubella outbreak started in the Netherlands in a population subgroup with low coverage, with subsequent spread to Canada.

Methods: We examined data on rubella cases in the Netherlands and Canada reported between September 2004 and July 2005. In The Netherlands we established enhanced surveillance for congenital rubella while in Canada we carried out a cohort study to estimate vaccine effectiveness.

Results: In The Netherlands and Canada, 387 and 309 rubella cases were reported, respectively. Of these, 97% were in unvaccinated individuals of orthodox protestant denomination. Reported consequences of rubella in pregnancy were 2 fetal deaths and 14 infants with congenital infection. Of the latter, 11 had clinical defects including deafness in all but eye defects in none. The estimated vaccine effectiveness was 99.3% (95% CI: 95.3%–99.9%). Closely related strains of rubella virus genotype 1G were found in Dutch and Canadian cases.

Conclusions: A large rubella outbreak occurred in The Netherlands with spread to Canada in a population subgroup with religious objections to vaccination. Its major public health importance was due to the high burden of congenital disease, international spread and implications for measles and rubella surveillance and elimination. Congenital deafness occurred more frequently and eye defects less frequently than expected. The estimated rubella vaccine effectiveness was very high. Our results demonstrate the risks associated with heterogeneity in rubella vaccine coverage. High rubella vaccine coverage in all population subgroups and sensitive surveillance are crucial for elimination of rubella and CRS.

Key Words: rubella virus, congenital rubella syndrome, vaccination, disease outbreaks

(*Pediatr Infect Dis J* 2009;28: 795–800)

Rubella during pregnancy can cause fetal growth retardation, abortion, and a wide range of fetal abnormalities which can present at birth, in infancy or later.[1–5] Since the late 1960s, rubella prevention became possible with the licensing of live, attenuated rubella vaccines, generally eliciting a protective immune response in 95% to 100% of recipients.[6] With adequate coverage a 2 dose rubella containing vaccine vaccination program can lead to the elimination of rubella.[7,8] Insufficient coverage of rubella vaccine, however, can lead to a increased incidence of congenital rubella.[9]

In the Netherlands and Canada, the rubella incidence dramatically decreased following the introduction of a 2 dose childhood measles, mumps, rubella vaccine (MMR) program (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A146). Since 1994, the estimated MMR coverage for 1 dose has not been below 95% in The Netherlands and 90% in Canada.[10,11] However, in both countries this overall figure conceals areas of lower coverage in communities who refuse vaccination for religious (orthodox protestant) reasons. Facilitated by socio-geographic clustering, several outbreaks of vaccine preventable diseases have occurred in these communities, including poliomyelitis in 1978 and 1992–1993, and measles in 1999–2000.[12–16] In 2004–2005 a rubella outbreak occurred in the orthodox protestant community in the Netherlands with subsequent spread to Canada.[17–19] We assessed the outbreak's burden of disease and characteristics, to identify opportunities to improve rubella control and surveillance.

Source: Hahné *PIDJ* 2009

RESEARCH

Main measles research areas at RIVM

Topic	Contact person
Early MMR - Literature review - Immunogenicity	Tom Woudenberg/Laura Nic Lochlainn Rob van Binnendijk
Transmission dynamics - School network modelling - Building a synthetic population	Jacco Wallinga
Phylogeny - nWGS to identify transmission chains: added value	Rogier Bodewes
Determinants of MMR vaccination - Effects of COVID-19 pandemic on MMR vaccine acceptance	Joyce Pijpers
Acceptance of MMR vaccination	Marijn Stok
Waste water surveillance - Added value?	Tom Woudenberg/Erwin Nagelkerke
Measles induced immunosuppression	Rik de Swart (Erasmus MC)

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Nature and *Science* publications on pathogenesis of measles immune suppression based on research in 2013/2014 outbreak

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07515-0 OPEN

Studies into the mechanism of measles-associated immune suppression during a measles outbreak in the Netherlands

Brigitta M. Laksono[1], Rory D. de Vries[1], R. Joyce Verburgh[1], Eline G. Visser[2], Alwin de Jong[1], Pieter L.A. Fraaij[1,2], Wilhemina L.M. Ruijs[3], David F. Nieuwenhuijse[1], Henk-Jan van den Ham[1,5], Marion P.G. Koopmans[1], Menno C. van Zelm[4,6], Albert D.M.E. Osterhaus[1,7] & Rik L. de Swart[1]

Measles causes a transient immune suppression, leading to increased susceptibility to opportunistic infections. In experimentally infected non-human primates (NHPs) measles virus (MV) infects and depletes pre-existing memory lymphocytes, causing immune amnesia. A measles outbreak in the Dutch Orthodox Protestant community provided a unique opportunity to study the pathogenesis of measles immune suppression in unvaccinated children. In peripheral blood mononuclear cells (PBMC) of prodromal measles patients, we detected MV-infected memory $CD4^+$ and $CD8^+$ T cells and naive and memory B cells at similar levels as those observed in NHPs. In paired PBMC collected before and after measles we found reduced frequencies of circulating memory B cells and increased frequencies of regulatory T cells and transitional B cells after measles. These data support our immune amnesia hypothesis and offer an explanation for the previously observed long-term effects of measles on host resistance. This study emphasises the importance of maintaining high measles vaccination coverage.

VIRAL IMMUNOLOGY

Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens

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Measles virus is directly responsible for more than 100,000 deaths yearly. Epidemiological studies have associated measles with increased morbidity and mortality for years after infection, but the reasons why are poorly understood. Measles virus infects immune cells, causing acute immune suppression. To identify and quantify long-term effects of measles on the immune system, we used VirScan, an assay that tracks antibodies to thousands of pathogen epitopes in blood. We studied 77 unvaccinated children before and 2 months after natural measles virus infection. Measles caused elimination of 11 to 73% of the antibody repertoire across individuals. Recovery of antibodies was detected after natural reexposure to pathogens. Notably, these immune system effects were not observed in infants vaccinated against MMR (measles, mumps, and rubella), but were confirmed in measles-infected macaques. The reduction in humoral immune memory after measles infection generates potential vulnerability to future infections, underscoring the need for widespread vaccination.

In the time before vaccination, nearly every child experienced measles, which resulted in millions of deaths. Global measles vaccination efforts have led to logarithmic reductions in the incidence of measles virus (MV) infections and measles-related mortality. However, measles remains endemic in much of the world, affecting >7 million people annually and causing >100,000 deaths (*1–3*). After decades of decline, the number of worldwide cases of measles has increased by nearly 300% since 2018 as a result of reduced vaccination (*2*). This increase is likely to be accompanied by substantial mortality risks (*3*). The resurgence of measles underscores the importance of understanding the full consequences of MV infection and accurately estimating the value of measles vaccination (*4*).

Immunosuppression was first documented when children with measles showed negative cutaneous tuberculin reactions after previously testing positive (*5*). Subsequent studies have shown decreased interferon signaling, skewed on total immunoglobulin G (IgG) levels (*7–12*). Recovery of the functional immune response, including resolution of lymphopenia, occurs 2 to 4 weeks after viral clearance (*6*, *10*, *13*, *14*). However, MV replication in immune cells has been hypothesized to impair immune memory, potentially causing "immunological amnesia" (*10*, *15*, *16*).

Most bona fide immune memory cells reside in the lymphoid tissues and bone marrow (*17–20*). Peripheral blood mononuclear cells are often used for evaluating immunological memory repertoires. However, these cells are in relative flux owing to recent infections, which limits their utility for measuring long-term immune memory. Antibodies are thought to better represent long-lived humoral memory (*18*, *20*). Most antibodies in the peripheral blood are produced by bone marrow long-lived plasma cells (LLPCs) and are impervious to disruptions in peripheral memory cells (*17–22*). Changes in pathogen-specific antibodies measured in the peripheral blood

childhood deaths from infectious diseases, mostly from non-MV infections (*15*). This phenomenon might be explained by immune amnesia. However, to date, no study has successfully resolved whether measles-induced immune amnesia—a reduction in the diversity of the immune memory repertoire after measles infections—indeed exists. To address this issue, we have studied paired blood samples collected before and after MV infection using a seroprofiling tool that allows the detection of thousands of pathogen-specific antibodies.

Measuring the consequences of measles on immune memory

During a recent measles outbreak in the Netherlands, families in communities with low vaccination rates consented to provide blood samples. Plasma was collected before and after laboratory-confirmed MV infection from 77 unimmunized children with a mean age of 9 (SD ± 2) years, plus five unimmunized children who remained uninfected during the study (*24*). Of the 77 children, 34 were reported to have mild measles and 43 to have severe measles [detailed in (*24*)]. The mean time between sample collections was 10 weeks, and mean time of collection after MV infection was 7 weeks (table S1).

To measure the diversity and magnitude of the epitope-specific antibody repertoires in these children and controls, we used VirScan (*25*), a phage-display immunoprecipitation and sequencing (PhIP-Seq) technology (*26*) developed for virome-wide detection of antibodies against viral epitopes. VirScan primarily detects antibodies to short contiguous epitopes as opposed to conformational epitopes. The cells producing antibodies to all epitopes are phenotypically similar, aside from their antibody product. Thus, changes in the antibody repertoire detected by VirScan represent changes across the spectrum of antibodies, and these include neutralizing and non-neutralizing antibodies. For this study, we generated an expanded VirScan library that encodes the full

Early MMR

- MMR-1 after 1 year of age probably optimal for high immunogenicity (WHO: 9-15 months of age)
  - no interference of maternal antibodies
  - immunological maturity
- In high-risk settings, WHO recommends a supplementary dose of MMR (MMR-0) from 6 months of age
- WHO technical consultation Dec 2023
  - Robust humoral immune response shortly after early MCV1 at 5-8 months of age.
  - Immune blunting of MCV2 after early MCV1 not demonstrated
  - However, 3-7 years after MCV1, those having received an early MCV1 had lower measles antibodies than children receiving MCV1 at routine age, suggesting faster waning of immunity.

Source: Varma et al, *Vaccine* 2025

Systematic literature reviews - 2015

Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis

Laura M Nic Lochlainn, Brechje de Gier, Nicoline van der Maas, Peter M Strebel, Tracey Goodman, Rob S van Binnendijk, Hester E de Melker, Susan J M Hahné

Summary

Background Measles is an important cause of death in children, despite the availability of safe and cost-saving measles-containing vaccines (MCVs). The first MCV dose (MCV1) is recommended at 9 months of age in countries with ongoing measles transmission, and at 12 months in countries with low risk of measles. To assess whether bringing forward the age of MCV1 is beneficial, we did a systematic review and meta-analysis of the benefits and risks of MCV1 in infants younger than 9 months.

Methods For this systematic review and meta-analysis, we searched MEDLINE, EMBASE, Scopus, Proquest, Global Health, the WHO library database, and the WHO Institutional Repository for Information Sharing database, and consulted experts. We included randomised and quasi-randomised controlled trials, outbreak investigations, and cohort and case-control studies without restriction on publication dates, in which MCV1 was administered to infants younger than 9 months. We did the literature search on June 2, 2015, and updated it on Jan 14, 2019. We assessed: proportion of infants seroconverted, geometric mean antibody titre, avidity, cellular immunity, duration of immunity, vaccine efficacy, vaccine effectiveness, and safety. We used random-effects models to derive pooled estimates of the endpoints, where appropriate. We assessed methodological quality using the Grading of Recommendations, Assessment, Development, and Evaluation guidelines.

Findings Our search identified 1156 studies, of which 1071 were screened for eligibility. 351 were eligible for full-text screening, and data from 56 studies that met all inclusion criteria were used for analysis. The proportion of infants who seroconverted increased from 50% (95% CI 29–71) for those vaccinated with MCV1 at 4 months of age to 85% (69–97) for those were vaccinated at 8 months. The pooled geometric mean titre ratio for infants aged 4–8 months vaccinated with MCV1 compared with infants vaccinated with MCV1 at age 9 months or older was 0·46 (95% CI 0·33–0·66; I^2=99·9%, p<0·0001). Only one study reported on avidity and suggested that there was lower avidity and a shorter duration of immunity following MCV1 administration at 6 months of age than at 9 months of age (p=0·0016) or 12 months of age (p<0·001). No effect of age at MCV1 administration on cellular immunity was found. One study reported that vaccine efficacy against laboratory-confirmed measles virus infection was 94% (95% CI 74–98) in infants vaccinated with MCV1 at 4·5 months of age. The pooled vaccine effectiveness of MCV1 in infants younger than 9 months against measles was 58% (95% CI 9–80; I^2=84·9%, p<0·0001). The pooled vaccine effectiveness estimate from within-study comparisons of infants younger than 9 months vaccinated with MCV1 were 51% (95% CI −44 to 83; I^2=92·3% , p<0·0001), and for those aged 9 months and older at vaccination it was 83% (76–88; I^2=93·8% , p<0·0001). No differences in the risk of adverse events after MCV1 administration were found between infants younger than 9 months and those aged 9 months of older. Overall, the quality of evidence ranged from moderate to very low.

Interpretation MCV1 administered to infants younger than 9 months induces a good immune response, whereby the proportion of infants seroconverted increases with increased age at vaccination. A large proportion of infants receiving MCV1 before 9 months of age are protected and the vaccine is safe, although higher antibody titres and vaccine effectiveness are found when MCV1 is administered at older ages. Recommending MCV1 administration to infants younger than 9 months for those at high risk of measles is an important step towards reducing measles-related mortality and morbidity.

Funding WHO.

Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis

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Lancet Infect Dis 2019; 19: 1246–54

Published Online September 20, 2019 https://doi.org/10.1016/S1473-3099(19)30396-2

See Comment page 1157

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Summary

Background Vaccinating infants with a first dose of measles-containing vaccine (MCV1) before 9 months of age in high-risk settings has the potential to reduce measles-related morbidity and mortality. However, there is concern that early vaccination might blunt the immune response to subsequent measles vaccine doses. We systematically reviewed the available evidence on the effect of MCV1 administration to infants younger than 9 months on their immune responses to subsequent MCV doses.

Methods For this systematic review and meta-analysis, we searched for randomised and quasi-randomised controlled trials, outbreak investigations, and cohort and case-control studies without restriction on publication dates, in which MCV1 was administered to infants younger than 9 months. We did the literature search on June 2, 2015, and updated it on Jan 14, 2019. We included studies reporting data on strength or duration of humoral and cellular immune responses, and on vaccine efficacy or vaccine effectiveness after two-dose or three-dose MCV schedules. Our outcome measures were proportion of seropositive infants, geometric mean titre, vaccine efficacy, vaccine effectiveness, antibody avidity index, and T-cell stimulation index. We used random-effects meta-analysis to derive pooled estimates of the outcomes, where appropriate. We assessed the methodological quality of included studies using Grading of Recommendation Assessment, Development and Evaluation (GRADE) guidelines.

Findings Our search retrieved 1156 records and 85 were excluded due to duplication. 1071 records were screened for eligibility, of which 351 were eligible for full-text screening and 21 were eligible for inclusion in the review. From 13 studies, the pooled proportion of infants seropositive after two MCV doses, with MCV1 administered before 9 months of age, was 98% (95% CI 96–99; I^2=79·8%, p<0·0001), which was not significantly different from seropositivity after a two-dose MCV schedule starting later (p=0·087). Only one of four studies found geometric mean titres after MCV2 administration to be significantly lower when MCV1 was administered before 9 months of age than at 9 months of age or later. There was insufficient evidence to determine an effect of age at MCV1 administration on antibody avidity. The pooled vaccine effectiveness estimate derived from two studies of a two-dose MCV schedule with MCV1 vaccination before 9 months of age was 95% (95% CI 89–100; I^2=12·6%, p=0·29). Seven studies reporting on measles virus-specific cellular immune responses found that T-cell responses and T-cell memory were sustained, irrespective of the age of MCV1 administration. Overall, the quality of evidence was moderate to very low.

Interpretation Our findings suggest that administering MCV1 to infants younger than 9 months followed by additional MCV doses results in high seropositivity, vaccine effectiveness, and T-cell responses, which are independent of the age at MCV1, supporting the vaccination of very young infants in high-risk settings. However, we also found some evidence that MCV1 administered to infants younger than 9 months resulted in lower antibody titres after one or two subsequent doses of MCV than when measles vaccination is started at age 9 months or older. The clinical and public-health relevance of this immunity blunting effect are uncertain.

Funding WHO.

Source: Nic Lochlainn, *Lancet Infect Dis*, 2019

Systematic literature reviews - 2016

- MMR-1 <6 months of age
  - Humoral immunogenicity dependent on age of MCV1
    - Increase in proportion seroconverted with age
    - Also dependent on presence of maternal antibodies and vaccine strain (Edmonston-Zagreb strain highest)
  - Cellular immunity, vaccine effectiveness and blunting
    - Limited evidence available
  - Data from the systematic review is insufficient to recommend vaccination under 6 months of age

Source: SAGE presentation October 2017

Systematic literature reviews – update 2025

- *Work in progress*

RIVM uptake study of early MMR (2013/2014)

- Using national vaccine register
- Uptake MMR-0: 57% among ≈10,000 invited infants
  - 70% uptake among those who had previous DTP
  - 1% uptake among those without previous DTP
- Risk factors for declining MMR-0 offer
  - High proportion SGP-votes
  - Unknown country of birth of parents
  - High SES (compared to very high SES)
- Conclusion
  - Those at highest risk did not accept MMR-0, 'worried well' did accept it?
- Challenges for public health:
  - Define the population at increased risk with high sensitivity and specificity
    - Measles outbreak*: 79% cases unvaccinated orthodox reformed (Rubella outbreak**: 97%)
  - Communicate risks and benefits to achieve higher uptake

Source: Nic Lochlainn, *Vaccine* 2017 *2013/2014 Woudenberg 2017 ** 2004/2005 Hahné 2009

RIVM immunogenicity studies of early MMR

- Set up during the 2013/2014 outbreak ('EMI' studies)
  - 79 children with MMR-0 at 6-12 months of age
  - 44 children with routine schedule (14 months & 9 years)
- Children vaccinated before 8.5 months of age:
  - Markedly faster antibody decay
  - Loss of protective neutralizing antibody levels after 6 years

Source: Van der Staak, CID, 2025

Early MMR group shows faster waning

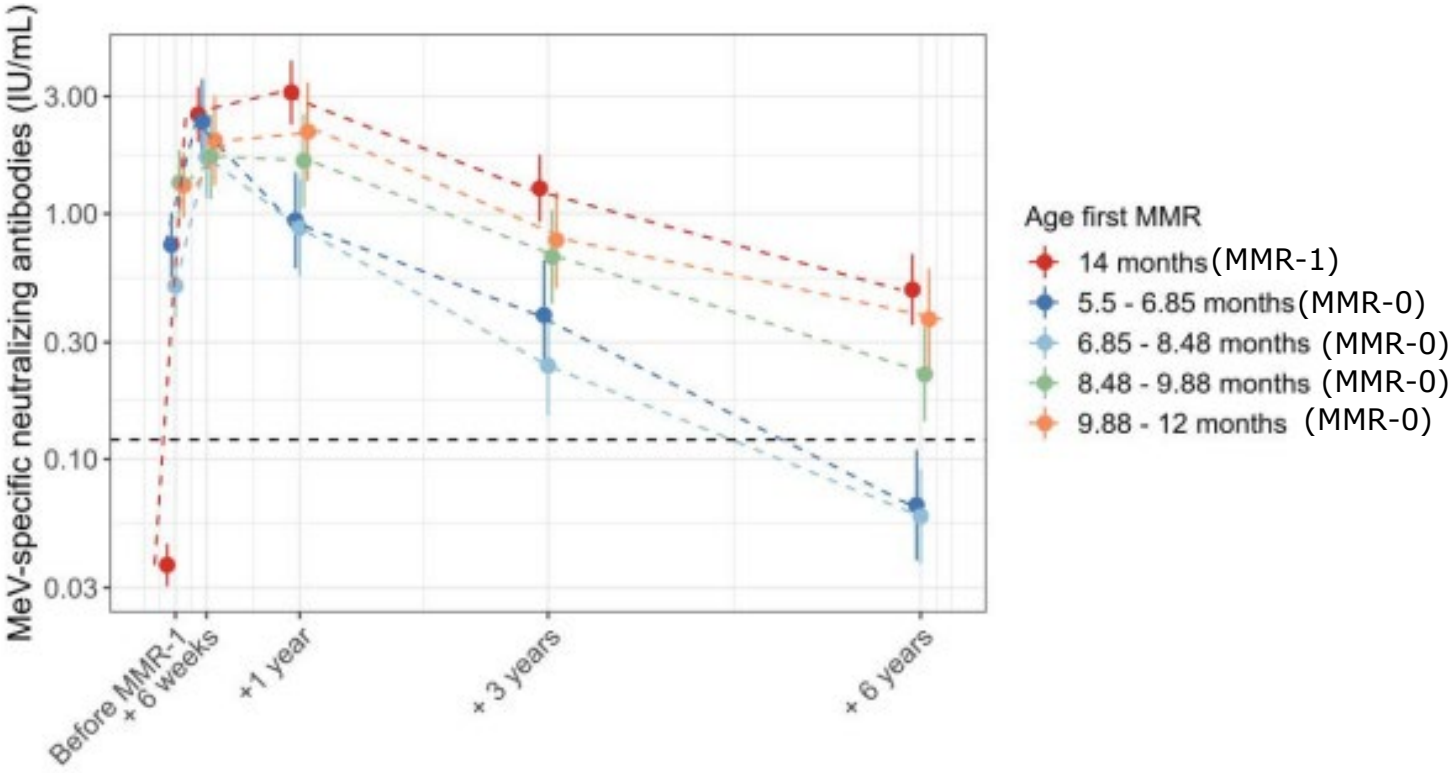
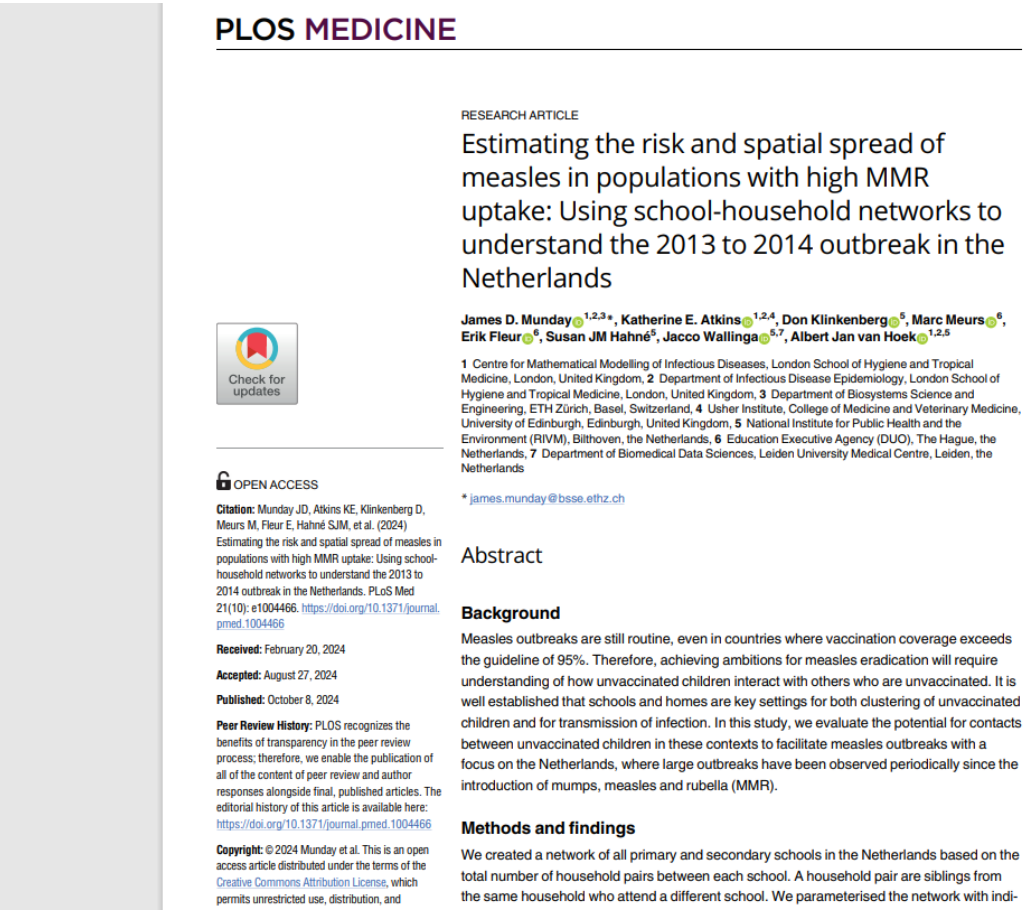


Figure 3. The model-predicted MeV-specific neutralizing antibody level averages shown as error bars with 95% CI of the different age groups. The dashed line the cutoff for protection against measles (0.12 IU/mL). In fitting this model, the children who received an early vaccination but were seronegative at 14 m excluded. Abbreviations: MeV, measles virus; MMR, measles, mumps and rubella.

Source: Van der Staak, CID, 2025

Mathematical modelling of school networks



PLOS MEDICINE

RESEARCH ARTICLE

Estimating the risk and spatial spread of measles in populations with high MMR uptake: Using school-household networks to understand the 2013 to 2014 outbreak in the Netherlands

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Abstract

Background

Measles outbreaks are still routine, even in countries where vaccination coverage exceeds the guideline of 95%. Therefore, achieving ambitions for measles eradication will require understanding of how unvaccinated children interact with others who are unvaccinated. It is well established that schools and homes are key settings for both clustering of unvaccinated children and for transmission of infection. In this study, we evaluate the potential for contacts between unvaccinated children in these contexts to facilitate measles outbreaks with a focus on the Netherlands, where large outbreaks have been observed periodically since the introduction of mumps, measles and rubella (MMR).

Methods and findings

We created a network of all primary and secondary schools in the Netherlands based on the total number of household pairs between each school. A household pair are siblings from the same household who attend a different school. We parameterised the network with indi-

Check for updates

OPEN ACCESS

Citation: Munday JD, Atkins KE, Klinkenberg D, Meurs M, Fleur E, Hahné SJM, et al. (2024) Estimating the risk and spatial spread of measles in populations with high MMR uptake: Using school-household networks to understand the 2013 to 2014 outbreak in the Netherlands. PLoS Med 21(10): e1004466. https://doi.org/10.1371/journal.pmed.1004466

Received: February 20, 2024

Accepted: August 27, 2024

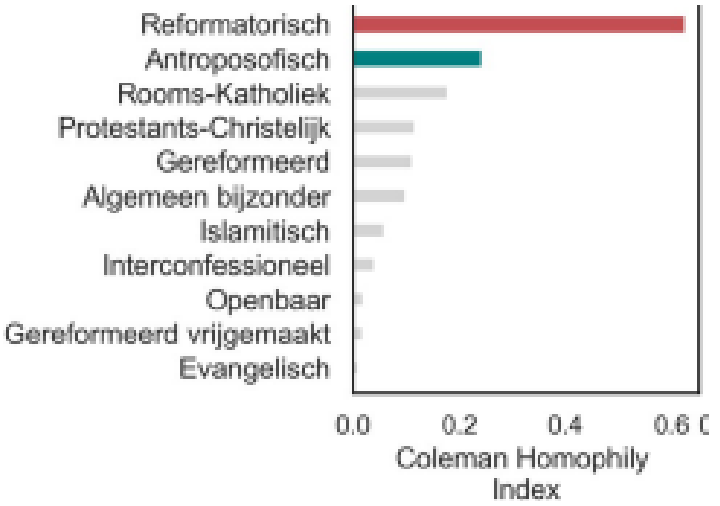
Published: October 8, 2024

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pmed.1004466

Source: Munday, *Plos Med* 2024

Mathematical modelling of school networks

- Network of all primary and secondary schools based on household information on siblings
- Measles transmission model applied to this network
- Data
  - individual level administrative school and household data
  - estimates of school level MMR uptake
- Results:
  - Orthodox reformed and Anthroposophic schools are highly connected
- Large outbreaks only occur when susceptible children in the same family attend primary and secondary schools
- Hence: interval between epidemics at least 12 years (next outbreak expected 2026)



Source: Munday, *Plos Med* 2024

INTERVENTIONS TO INCREASE UPTAKE

Interventions to increase uptake

- Orthodox reformed community
  - Conversation from a religious perspective
  - Current priority: Rubella!
- Low vaccine coverage pockets in large cities
  - Community based approaches
  - Communities of practice
- The key is prioritization
  - Seroepidemiology
  - Epidemiologic research
  - Mathematical modelling

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Conversations with orthodox reformed individuals about vaccination

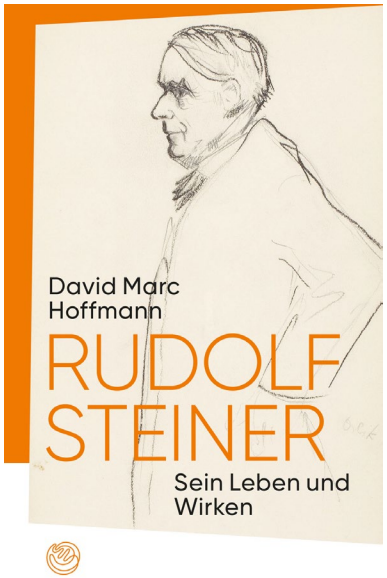
- PhD Helma Ruijs (2012)
  - Collaboration with NPV
  - 'Dutch Patient Society'
  - Christian NGO
- Orthodox protestant discourse around three main themes
  - Divine providence
  - Trust
  - Responsibility

2021

2012

Anthroposophical discourse about influenza vaccination

- **Example: Invitation from a Dutch Anthroposophic GP for influenza vaccination**
- ***'Why get a flu shot?***
  - For vulnerable elderly, flu is a serious illness. Moreover, flu can destabilize diabetes, worsen heart conditions, or lead to pneumonia.
  - To protect others: for example, if you frequently visit a vulnerable person.
- ***'Why not get a flu shot?'***
  - Flu can be a moment of rest, reflection, and reordering. After recovering from flu, one may feel refreshed and ready for a new start.
  - Good nutrition, low stress, and plenty of physical activity reduce susceptibility to infections.



Source: B. Zevenbergen, Zeist, The Netherlands, October 2025

Current priority: CRS prevention among orthodox reformed women of childbearing age

- Currently women of childbearing age in OR community are less well protected than their mothers
  - long interepidemic interval; less natural immunity
  - they are likely not aware of this
- Risk assessment
  - Susceptible ages now 0-24 whereas prior to the 2004/2005 outbreak it was 0-18 (seroepidemiology)
  - Reduced change of introduction of rubella
- PH responsibilities and actions?
  - Duty to inform these women about changed risk profile
  - Need for active outreach with MMR vaccination offer?
  - Meeting to advise Government: 20 October 2025
- Adequate rubella and vaccine coverage surveillance suffices for risk assessment
- Vaccine Register allows inviting target group individually by mail

SYNTHESIS

Synthesis

- Heterogeneous vaccine coverage leads to outbreaks with large 'preventable' burden and international implications due to migration history
- In the Netherlands: Very extensive insights into the mechanisms
  - SGP voting proportions
  - Nationwide registers: vaccine register, denominational school registers
  - Seroepidemiology and surveillance
  - Mathematical modelling
  - Laboratory studies
- Opportunities for prevention limited; adapt discourse to target group
  - Early MMR: all about targeting well
  - Rubella may be the first example where we take a pro-active approach
- Plenty of opportunities for research with international relevance
- Stigmatization vs optimal epidemiology and targeted communication
  - Moral debate methods
  - Improve the proxies we use as epidemiologists

Acknowledgements

Municipal Health Service Colleagues

RIVM & Erasmus MC

Jacco Wallinga

Joyce Pijpers

Hester de Melker

Tom Woudenberg

Helma Ruijs

Rogier Bodewes

Rob van Binnendijk

Rik de Swart