

**Measles transmission from vaccinated cases -
Systematic Review Protocol**

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Conflicts of interest - The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: WO is a consultant with Merck, Sanofi, Moderna, Dynavax, and Seqirus, however receives no funding related to the subject of this manuscript. The Centre for Vaccine Preventable Diseases (CVPD), of which SB is Director, is supported by various funding sources, including donations from vaccine manufacturers. The CVPD has a robust set of governance processes at the University of Toronto to ensure independent operation of the Centre and its Faculty and Staff. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

INPLASY registration number: INPLASY2025110004

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 November 2025 and was last updated on 2 November 2025.

INTRODUCTION

Review question / Objective 1. Is there evidence of measles transmission from vaccinated cases?

2. What are the characteristics* of vaccinated individuals who transmit measles; the cases infected by vaccinated individuals; and the settings in which transmission occurs? What are the laboratory findings (e.g. RNA detection, IgG avidity etc)

3. What is the impact of transmission from vaccinated cases, as measured by a) the average or median number of infections originating from a vaccinated case, b) the number of subsequent generations, and c) size of outbreak with vaccinated individual as index case?

4. What is the effectiveness of measles vaccine against infectiousness?

* i.e. – age, sex, case definition, type of MCV received, clinical presentation, number of doses received, age at first dose, age at second dose.

Rationale Measles is one of the most infectious cause of vaccine-preventable disease cases and deaths (1). Efforts to achieve measles elimination, defined as the absence of endemic transmission for ≥ 12 months, are led by the World Health Organization (WHO), which set a target in 2015 to eliminate measles in at least five of the six WHO Regions by 2020 (2). Achieving measles elimination requires two doses of measles containing vaccine (MCV) to be administered with very high coverage. Immunity following measles vaccination is thought to perhaps be shorter than immunity from previous infection, but still provides protection for decades (3).

As countries work towards and achieve measles elimination and measles cases decline, the proportion of their populations protected through vaccination increases each year as infants are born and are vaccinated, while the proportion of the population immune through previous infection continuously decreases, as older individuals, who had measles long ago when they were children, die. However, vaccine-derived immunity is less robust than immunity from previous infection, with antibody levels declining slowly over time (4-6). Over time, waning immunity may be accelerating due to a lack of immunological boosting from circulating virus, potentially resulting in immune individuals becoming susceptible over time (5), a phenomenon known as secondary vaccine failure. The combination of an ever-increasing proportion of vaccinated individuals and waning vaccine-derived immunity would not be an issue if all countries were on track to eliminate measles. However, while some countries eliminated measles decades ago, including Finland, Canada, and the United States, measles is currently not eliminated in any WHO region (7). Although the Americas achieved measles elimination in 2016, it subsequently lost its elimination status in 2018 when endemic measles transmission was re-established in Venezuela. This was followed by loss of elimination status in Brazil in 2019 (8). In recent years, several other countries lost their elimination status, including the United Kingdom, Greece, Czech Republic, Albania, Brazil, Venezuela and Mongolia (9), providing an opportunity for continued global circulation and importation. To achieve measles eradication (or worldwide elimination), countries/regions need to sustain elimination over many years. The scenario of waning vaccine immunity in eliminated jurisdictions, set against a backdrop of repeated measles importations from high-incidence countries presents a critical challenge to sustaining measles elimination, particularly if cases experiencing primary or secondary vaccine failure can transmit their infection to others. This would

potentially result in outbreaks and even jurisdictional loss of elimination status in settings with a high proportion of individuals immune through vaccination, if vaccinated persons can sustain transmission.

This systematic review aims to review evidence for measles transmission from vaccinated cases, assess the extent to which transmission from vaccinated cases has contributed to measles outbreaks, and describe the size of any resulting outbreaks. If possible, we will assess measles vaccine effectiveness against infectiousness.

Condition being studied Measles vaccine failure.

METHODS

Search strategy We used Medline, EMBASE, Global Health, BIOSIS reviews, Science Citation Index.

Search terms (list is not exhaustive:

- Measles/ or Measles Virus/ or Measles Vaccine/
- (Morbillivirus Infections/ or Morbillivirus/ or Measles-Mumps-Rubella Vaccine/) and (measles or (edmonston adj3 virus*) or rubeola).
- (measles or (edmonston adj3 virus*) or rubeola).kf,kw,ti.
- (morbillivirus* or moraten or (schwartz and strain*) or "Leningrad-16" or "Shanghai-191" or "CAM-70" or "AIK-C" or "TD97" or MCV or MCVs or MMR or MMR1 or MMR2 or MMRI or MMRII or MMRV or MMRV1 or MMRV2 or MMRVI or MMRVII).kf,kw,ti. and (measles or (edmonston adj3 virus*) or rubeola).ab,kf,kw,ti.
- (measles or (edmonston adj3 virus*) or rubeola).ab. /freq=2 not medline.st.
- ((morbillivirus* or moraten or (schwartz and strain*) or "Leningrad-16" or "Shanghai-191" or "CAM-70" or "AIK-C" or "TD97" or MCV or MCVs or MMR or MMR1 or MMR2 or MMRI or MMRII or MMRV or MMRV1 or MMRV2 or MMRVI or MMRVII).ab. /freq=2 and (measles or (edmonston adj3 virus*) or rubeola).ab,kf,kw,ti.) not medline.sb.
- Disease Transmission, Infectious/ or Measles/tm or Infectious Disease Transmission, Patient-to-Professional/ or Infectious Disease Transmission, Professional-to-Patient/ or Disease Outbreaks/ or Cross Infection/ or Virus Shedding/ or Carrier State/
- (carrier* or cluster* or communicab* or contagious* or epidemic* or excret* or infected or infect or infects or infecting or infectious* or infectiv* or (infection* adj3 route*) or outbreak* or shed* or transmi* or transmissibility or ((acquir* or acquisition or catch* or caught or contract* or get*

or got* or occurrence or spread*) adj3 measles) or "index case*").kf,kw,ti.

– (carrier* or cluster* or communicab* or contagious* or epidemic* or excret* or infected or infect or infects or infecting or infectious* or infectiv* or (infection* adj3 route*) or outbreak* or shed* or transmi* or transmissibility or ((acquir* or acquisition or catch* or caught or contract* or get* or got* or occurrence or spread*) adj3 measles) or "index case*").ab. /freq=2

– (vaccinated or immunized or immunised).ab,kf,kw,ti.

– ("vaccination status" or "high vaccination coverage").ab,kf,kw,ti.

– ("evidence of prior immunity" or "prior evidence of immunity").ab,kf,kw,ti.

– (postvaccin* or postimmuniz* or postimmunis* or "post vaccin*" or "post-immuniz*" or "post-immunis*").ab,kf,kw,ti.

("measles elimination" or "elimination setting*" or "elimination status" or "post elimination" or postelimination).ab,kf,kw,ti.

– (((recipient* or document*) adj5 (vaccin* or immuniz* or immunis* or dose or doses or MCV or MCVs or MMR*)) or (document* adj3 immunity)).ab,kf,kw,ti.

– ((receiv* or already or post or previously or after or following or "subsequent to" or since or have or had) adj5 (vaccin* or immuniz* or immunis* or dose or doses or MCV or MCVs or MMR*) adj5 (person or persons or people or individual or individuals or man or men or woman or women or boy or boys or girl or girls or student or students or adult or adults or adolescent or adolescents or child or children or patient or patients or case or cases or population or populations or community or communities or group or groups)).ab,kf,kw,ti.

Participant or population – Individuals ≥ 9 months of age.

Intervention Measles vaccine.

Comparator – In studies that report vaccinated and unvaccinated cases, compare to transmission from unvaccinated cases (to ensure setting is comparable)

– In studies where this information is not available, compare to the hypothesis that vaccinated cases do not transmit.

Study designs to be included - Case control or cohort studies describing outbreak investigations or that calculate vaccine effectiveness Peer reviewed observational studies, primary data

studies, also grey literature (ie - surveillance reports).

Eligibility criteria For title abstract screening, studies were included if they included:

- Description of measles outbreak
- Specific mention of measles in vaccinated cases
- Mention of vaccine effectiveness estimates
- Mention of transmission from a vaccinated individual
- Reference to chain of transmission being created
- Mention of vaccine failure

For full text screening, studies were included if they had:

- Study describes measles transmission from a vaccinated case.
- Studies with limited data on number of doses or age of cases will be included, but quality issues will be noted.

Information sources Bibliographic databases, web browsers, screening reference lists of included studies, consulting with co-investigators to identify relevant studies that should be screened.

Main outcome(s) Transmission from vaccinated individual and their characteristics.

Data management Data will be managed using systematic review software.

Quality assessment / Risk of bias analysis The quality of included papers will be assessed using a bespoke checklist developed for this systematic review. Papers will be evaluated against a number of expected items including, among others: whether measles infection was confirmed through laboratory testing; whether information was provided on the number of previous measles doses received; whether a full description of the measles outbreak was reported; and what was the source of vaccination status information among cases. Additional quality appraisal tools (e.g. the Critical Appraisal Skills Programme (CASP) Case Control Study Checklist, CASP Cohort Study Checklist, Consolidated Standards of Reporting Trials Statement (CONSORT), etc.) may be used alongside our tool for validity appraisal if necessary.

We will use the Guide to Appraising Grey Literature, authored by the Public Health Ontario Library Services team, to assess each grey literature article selected for inclusion in the review. During quality appraisal, we may exclude a study if

we appraise it to be of low quality, or if we find substantial methodological issues. To determine risk of bias we will refer to the Cochrane ROBINS-I tool to determine the main sources of bias across all studies included in our review for each research question. If required, we will then conduct sensitivity analyses by removing any studies with either a high risk of bias or low quality, or both, and re-running our analyses.

Strategy of data synthesis Following data extraction, we will synthesize and analyze the data, and will also conduct a meta-analysis, if appropriate, to summarise transmission dynamics such as mean number of transmissions from vaccinated cases, number of subsequent generations, mean outbreak size caused by vaccinated index cases, and the frequency of transmission from cases who experience primary vs. secondary vaccine failure. We will use Microsoft Excel, DistillerSR, and Stata for analyses and figure generation. Where possible, we will present our results in graphical form.

We will conduct synthesis and analyses to characterize both measles vaccinated cases who transmit, and the individuals to whom they transmit in order to inform more tailored approaches to close immunity.

We will assess the ability to meta-analyze the data by examining the clinical, methodological, and statistical heterogeneity of studies and the impact of effect modifier variables on effect sizes using meta-regression models where necessary. A value of 75% will be used to indicate high levels of statistical heterogeneity (I²). We will generate funnel plots to assess the possibility of publication bias (if >10 studies are identified for analyses). If possible, sensitivity and subgroup analyses will be conducted to compare results with and without studies of lower quality.

Subgroup analysis We will analyze by number of vaccine doses and whether the case took place in an endemic or eliminated measles.

Sensitivity analysis None.

Language restriction English only.

Country(ies) involved Canada, US, Netherlands, Australia.

Keywords Measles, measles vaccine, vaccine failure.

Dissemination plans We will submit the systematic review to a peer-reviewed manuscript.

Contributions of each author

Author 1 - James Wright - JW was responsible for Investigation (literature search); Methodology; data curation (literature screening and extraction); formal analysis; data visualization; Project administration; writing – original draft. NSC was responsible for conceptualization; Methodology; writing – review & editing.

Author 2 - Natasha Crowcroft - NC was responsible for conceptualization; Methodology; writing – review & editing.

Author 3 - Julie Perry - JP was responsible for Investigation (literature search); Methodology; data curation (literature screening and extraction); writing – review & editing.

Author 4 - Heili Poolsaar - HP was responsible for Investigation (literature search); Methodology; data curation (literature screening and extraction); writing – review & editing.

Author 5 - Paul Gastañaduy - Involved in conceptualization; Investigation; writing – review & editing.

Author 6 - David Durrheim - Involved in conceptualization; Investigation; writing – review & editing.

Author 7 - William Moss - Involved in conceptualization; Investigation; writing – review & editing.

Author 8 - Susan Hahne - Involved in conceptualization; Investigation; writing – review & editing.

Author 9 - Walter Orenstein - Involved in conceptualization; Investigation; writing – review & editing.

Author 10 - Paul Rota - Involved in conceptualization; Investigation; writing – review & editing.

Author 11 - Selma Osman - Responsible for literature search; data curation (literature screening and extraction); writing – review & editing.

Author 12 - Desiree Pastor - Involved in conceptualization, writing – review & editing.

Author 13 - Alberto Severini - Involved in conceptualization, writing – review & editing.

Author 14 - Shelly Bolotin - SB was responsible for conceptualization; Investigation; methodology; project administration; supervision; writing – original draft; writing – review & editing.