RESEARCH DRAFT PROTOCOL

TITLE: Public Health Interventions to Reduce Secondary Spread of Measles

DATE: DRAFT 23 October 2014

CONTEXT AND POLICY ISSUES

Measles is a highly communicable infectious disease that is spread through droplets from the nose or throat, e.g., via coughing or sneezing. There are limited treatments beyond supportive care. However, measles is preventable by immunization. Symptoms of measles are high fever, runny nose, cough, conjunctivitis, drowsiness, irritability and a red blotchy rash that starts on the face and spreads to the body and limbs; symptoms may develop seven to 21 days after exposure to an infected person. Measles is highly contagious from four days before to four days after the onset of rash. Complications are rare but can be serious including blindness, encephalitis, and severe respiratory infections like pneumonia.

Routine publicly-funded measles vaccine programs were implemented in Canada in the early 1970s and were widely provided since the early 1960s in at least Ontario. By 1983, rubella and mumps were added to the routine schedules with one dose of the combined measles-mumps-rubella (MMR) vaccine. The next step was for provinces and territories to add a second dose of MMR to their routine schedules which was completed by 1997. Vaccination programs have eliminated measles in Canada; however, importations and outbreaks continue to occur due to (a) travel to countries with disease activity and (b) susceptible individuals and communities who are unimmunized or underimmunized.

Five public health interventions that may be used to reduce secondary spread of measles are:

- Vaccination of identified susceptible contacts within 72 hours of contact or exposure.
- Administration of immunoglobulin to identified susceptible contacts within six days of contact or exposure.
- Quarantine or exclusion of susceptible contacts.
- Isolation or exclusion of those infected with measles.
- Vaccination clinics or activities above and beyond routine vaccination services to increase population immunization coverage, e.g., extended hours of immunization services and mobile units to provide additional vaccination services. Vaccination clinics can be a “targeted immunization activity”; this refers to vaccination clinics established in response to a measles outbreak that target a specific population, e.g., by age, immunization status or specific geographic location.

The order of intervention tends to occur by what is appropriate given the timeline following exposure. Typically, vaccine is the first choice of intervention (if within 72 hours of exposure), followed immunoglobulin (if after 72 hours but within six days following exposure) followed by isolation / quarantine / exclusion (if the exposure has exceeded six days). Exceptions do occur, e.g., the vaccine may be contraindicated for a susceptible contact.
Public health interventions are applied through the process of contact tracing that results in a list of susceptible contacts for which an assessment of the most appropriate intervention is completed. Further, in some cases, vaccine clinics may be established by local public health personnel when transmission has spread to a point where identifying susceptible contacts is no longer feasible. These clinics also serve as opportunities to increase population coverage for measles-containing vaccine.

The objective of this study is to conduct a systematic review of the clinical evidence on the effectiveness of public health interventions in reducing the secondary spread of measles.

**RESEARCH QUESTIONS**

1. What is the effectiveness associated with delivery of measles vaccine to susceptible measles contacts?
2. What is the effectiveness associated with immunoglobulin delivery to susceptible measles contacts?
3. What is the effectiveness associated with quarantine of susceptible measles contacts?
4. What is the effectiveness associated with isolation of communicable measles cases?
5. What is the effectiveness of targeted measles vaccination activities during an outbreak?

**METHODS**

**Literature search strategy**

The literature search will be performed by an information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following bibliographic databases: MEDLINE with in-process records and daily updates via Ovid, EMBASE via Ovid, Cochrane Central via Ovid, and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts will be outbreak response methods (vaccine delivery, immunoglobulin delivery, quarantine, isolation and targeted vaccination activities) and measles.

No methodological filters will be applied to limit retrieval by publication type. Where possible, retrieval will be limited to humans. The search will also be limited to English and French language documents published between January 1, 1994 and September 25, 2014. Regular alerts will be established to update the search until project completion. Conference abstracts will be excluded from the search results. See Appendix 1 for the detailed search strategies.

Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the Grey Matters checklist ([http://www.cadth.ca/resources/grey-matters](http://www.cadth.ca/resources/grey-matters)). Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and, if need be, through contacts with appropriate experts. See Appendix 1 for more information on the grey literature search strategy.
Article selection

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria (Table 1), will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen included/excluded studies. Disagreements will be resolved through discussion until consensus is reached. Duplicate publications of the same trial will be excluded unless they provide additional outcome information of interest. The study selection process will be presented in a PRISMA flowchart.

Table 1: Literature Selection Criteria

| Populations | • All ages  
| • Countries or WHO Regions:  
| (a) Americas (PAHO): all countries;  
| (b) Europe: Andorra, Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, UK;  
| (c) Western Pacific: Australia, New Zealand  
| • Questions 1 to 3: Susceptible individual who has come into contact with a confirmed/probable/clinical case of measles (outbreak, importation, exposure on a conveyance)  
| • Question 4: Person with confirmed/probable/clinical measles  
| • Question 5: Patient targeted by the clinic’s target population, e.g., by age, immunization status or geographic location |
| Interventions | Question 1: Vaccine delivery (all forms and schedules of vaccine)  
| Question 2: Immunoglobulin delivery (all forms and schedules of immunoglobulins)  
| Question 3: Quarantine for susceptible contacts (until the incubation period has ended for non-cases, or until the period of communicability has ended for all cases)  
| Question 4: Isolation for those with the virus (until the period of communicability has ended)  
| Question 5: Vaccine delivery to those identified in the clinic (includes potential non-contacts) |
| Comparators | Question 1: No vaccine delivery  
| Question 2: No immunoglobulin delivery  
| Questions 3 and 4: No isolation/quarantine strategies  
| Question 5: No vaccination clinic, i.e., regular vaccination activities that would occur in the absence of an outbreak |
| Outcomes | Number (and/or incidence) of confirmed measles cases, number of probable measles cases, number of hospitalizations due to measles or measles-related complications, and number of deaths due to measles or measles-related complications |
| Study types | Randomized controlled trials and non-randomized studies with a control group |

* Year limits: 1994 for PAHO countries, 1999 for European Region, 2005 for Western Pacific Region. (These are the years when the regions committed to regional measles elimination goals — selected as proxy indicators of the likely public health efforts to respond to measles importations/outbreaks.)
Exclusion Criteria

Articles will be excluded if they do not meet the selection criteria in Table 1, if they were published prior to January 1994, or if they are duplicate publications of the same study. In particular, the following will be considered out of scope:

- **Population**: Susceptible individuals in countries with poor vaccination rates who do not have similar public health systems / guidelines in place to respond to measles outbreaks (the definition of “susceptible contact” can vary greatly from the Canadian definition).

- **Interventions**: Interventions to treat measles (e.g., vitamin A injections), different registry / surveillance activities, effectiveness of different vaccinations / schedules of vaccinations, and adverse events from vaccination.

- **Comparators**:
  - Question 1: Effectiveness across different vaccines plus different definitions of susceptible contacts.
  - Question 2: Effectiveness across different definitions of susceptible contacts.
  - Questions 3 & 4: Effectiveness across different isolation strategies including different timing of isolation strategies plus different definitions of susceptible contacts.
  - Question 5: Effectiveness across different clinic variables plus different definitions of susceptible contacts.

- **Outcomes**: Effectiveness of vaccines in routine/no measles outbreak scenario (primary prevention), effectiveness of immunoglobulin provided in routine/no measles outbreak scenarios, adverse events of routine/scheduled vaccinations of the population, morbidity/adverse effects of measles other than those specified in the selection criteria, and comparative effectiveness of strategies by a manufacturer.

- **Study types**: Ecological or modelling studies and case reports.

Data extraction and critical appraisal

Extracted data will adhere to the outcomes identified in Table 1. Data will be extracted independently by two reviewers and any disagreements will be resolved through discussion until consensus is reached. One reviewer will use the validated Downs and Black checklist\(^3\) to assess the study quality of RCTs and non-randomized studies based on quality of reporting, external validity and risk of bias. Numeric scores will not be reported; instead a narrative and tabular description of the strengths and limitations of each included study will be presented.

Data analysis methods

If RCTs are available, results will be pooled by outcome, where applicable. If meta-analysis is deemed inappropriate due to either heterogeneity of the clinical (based on patients characteristics and demographics, similarity of interventions and comparators) and methodological characteristics (based on study design and outcomes definition) of included studies, or for non-randomized trials a narrative synthesis (including patient characteristics, interventions, comparators, outcomes and study design) and summary of study findings will be
conducted instead. If meta-analysis is deemed appropriate, meta-analyses will be carried out using Cochrane Review Manager software to derive pooled estimates of interest. If sufficient homogeneity is found across trials, all meta-analyses performed will consider fixed effect model; if not, a random effects model will be used. Forest plots will be presented for all evidence syntheses to supplement reported estimates. Analyses of dichotomous outcomes will be summarized using relative risks and 95% confidence intervals, and analyses of continuous outcomes will be summarized using mean differences and 95% CI. The chi-square test will be used to assess effect size variance, with P < 0.10 indicating significant heterogeneity across trials.

When significant heterogeneity is identified and sufficient data are available, subgroup analyses will be conducted to identify the primary sources of heterogeneity, such as patient characteristics and intervention procedure. Additional sensitivity analyses will also be considered to establish the robustness of findings, e.g., dealing with outlying data points, study quality, study size, and other factors. If required measures of variance are found to be missing from a relevant article, the study's authors will be contacted to determine if the measure can be provided for the purposes of this investigation. If relevant data are not available, variances will be imputed where possible.

Subgroup Analyses

- If possible, subgroup analyses will be conducted on the effectiveness of (a) vaccine or (b) immunoglobulin delivery to susceptible contacts based on number of received/reported received doses (0, 1) of measles-containing vaccine (including MMR or MR).

- If possible, subgroup analyses will be conducted on the effectiveness of vaccine and immunoglobulin delivery versus outside the recommended timeframes. (The recommended timeframe for vaccine is within 72 hours of exposure and the recommended timeframe for immunoglobulin is within 6 days of exposure.)

- If possible, subgroup analyses will be provided for immunoglobulin to recognize the different strengths of concentration (as this changed over time).

If possible, subgroup analyses will be conducted on high risk contacts versus other contacts, number of hospitalizations due to measles or measles-related complications, and number of deaths due to measles or measles-related complications.
References


APPENDIX 1: LITERATURE SEARCH STRATEGY

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<th>OVERVIEW</th>
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<td>Interface:</td>
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<td>Databases:</td>
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<td>Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.</td>
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<td>Date of Search:</td>
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<td>Alerts:</td>
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<td>Study Types:</td>
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<th>SYNTAX GUIDE</th>
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Multi-database Strategy

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<tr>
<td>1</td>
<td>Measles/ or Measles virus/ or exp Measles vaccine/</td>
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<tr>
<td>2</td>
<td>(measle* or rubeola or morbillivirus or morbilli).ti,ab.</td>
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<td>3</td>
<td>1 or 2</td>
</tr>
<tr>
<td>4</td>
<td>Contact tracing/</td>
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<td></td>
<td>(contact* adj4 (trac* or identif* or detect* or exam* or name* or case* or control or trace or tracing or infection*</td>
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<td></td>
<td>or infected or pattern* or casual or intimate or information or investigation* or passenger* or household* or</td>
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<td></td>
<td>follow up or followed up or immunocompromised or immune-compromised or high risk or case-patient)).ti,ab.</td>
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<td>5</td>
<td>contacts.ti,ab. or contact*.ti. or time to contact.ti,ab. or susceptible.ti. or susceptibles.ti,ab.</td>
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<td>6</td>
<td>(susceptible adj3 (individual* or contact* or case* or person* or people or adult* or women or men or child* or</td>
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<td></td>
<td>employee* or student* or subgroup* or sub-group* or infant* or adolescen* or teen* or youth or youths or</td>
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<td>population* or communit*)).ti,ab.</td>
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<tr>
<td>7</td>
<td>(suspected adj3 (patient* or case* or contact*)).ti,ab.</td>
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<tr>
<td>8</td>
<td>(measle* adj2 (exposed or exposure)).ti,ab.</td>
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<td>9</td>
<td>(unimmuniz* or unimmunis* or underimmuniz* or underimmunis* or under-immuniz* or under-immunis* or</td>
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<td></td>
<td>unvaccinat* or undervaccinat* or under-vaccinat* or non-vaccinat* or un-vaccinat* or</td>
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<td></td>
<td>unvaccinat* or un-immuniz* or un-immunis*).ti,ab.</td>
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<td>10</td>
<td>(&quot;not&quot; adj2 vaccinated).ti,ab.</td>
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<td>11</td>
<td>(fail* adj4 vaccinat*).ti,ab.</td>
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<td>12</td>
<td>(secondary adj2 (spread or attack* or transmission*)).ti,ab.</td>
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<tr>
<td>13</td>
<td>(case adj (finding or detect* or identif*)).ti,ab.</td>
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<tr>
<td>14</td>
<td>or/4-14</td>
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<td>Hospitals, Isolation/ or Patient isolation/ or Patient isolators/ or Quarantine/ or isolation.ti.</td>
</tr>
<tr>
<td>16</td>
<td>Isolat*.ti,ab. and (Cross Infection/ or exp Disease Transmission, infectious/ or exp Disease outbreaks/ or exp</td>
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<td></td>
<td>Communicable Diseases/ or Infection Control/)</td>
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<tr>
<td>17</td>
<td>(Isolat* and (cross infection or nosocomial* or infection control or outbreak* or hospital acquired or healthcare</td>
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<td></td>
<td>associated or health care associated or hospital associated or communicable)).ti,ab.</td>
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<tr>
<td>18</td>
<td>(isolat* and (import* adj4 (case or cases or virus or disease))).ti,ab.</td>
</tr>
<tr>
<td>19</td>
<td>((Isolator* or isolation or isolating or isolate or isolated or segregat* or containment) adj3 (patient* or ward* or</td>
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</table>
Public Health Interventions to Reduce Secondary Spread of Measles

unit* or room* or precaution* or pre-caution* or preemptive or pre-emptive or contact* or practice* or measure or measures or facility or facilities or period* or strateg*).ti,ab.

(quarantin* or quarantain* or cohorting or cohort nursing or superisolation or isolette* or droplet precaution* or reverse isolation).ti,ab.

or/16-21

exp Vaccination/ or exp Immunoglobulins/ or exp Measles vaccine/

(vaccinat* or immuniz* or immunis* or immunoglobulin* or immune globulin* or vaccine* or inoculat*).ti,ab.

23 or 24

exp Disease outbreaks/

23 (outbreak* or importation* or secondary spread or secondary transmission*).ti,ab.

23 ((epidemic* or pandemic*) adj4 measle*).ti,ab.

26 or 27 or 28

((target* or outbreak*) adj3 (response* or campaign* or strateg*)).ti,ab.

26 or 27 or 28

29

30 or 31

3 and (15 or 22)

34

3 and 29

35

3 and 32

36

33 or 34 or 35

37 exp Measles/ or Measles vaccination/ or Measles vaccine/

38 (measle* or rubeola or morbillivirus or morbilli).ti,ab.

39

37 or 38

40 Contact examination/ or Susceptible population/

41 (contact* adj4 (trac* or identifi* or detect* or exam* or name* or case* or control or infection* or infected or pattern* or casual or intimate or information or investigation* or passenger* or household* or follow up or followed up or immunocompromised or immune-compromised or high risk or case-patient)).ti,ab.

42 contacts.ti,ab. or contact*.ti. or time to contact.ti,ab. or susceptible.ti. or susceptibles.ti,ab.

(susceptible adj3 (individual* or contact* or case* or person* or people or adult* or women or men or child* or employee* or student* or subgroup* or sub-group* or infant* or adolescent* or teen* or youth or youths or population* or community* or group* or household* or family* or communit*)).ti,ab.

(suspected adj3 (patient* or case* or contact*)).ti,ab.
Public Health Interventions to Reduce Secondary Spread of Measles

(measle* adj2 (exposed or exposure)).ti,ab.
(unimmuniz* or unimmunis* or underimmuniz* or under-immuniz* or under-immuniz* or
unvaccinat* or undervaccinat* or under-vaccinat* or non-vaccinat* or nonvaccinat* or un-vaccinat* or
unvaccinat* or un-immuniz* or un-immunis*).ti,ab.
("not" adj2 vaccinated).ti,ab.
(fail* adj4 vaccinat*).ti,ab.
(secondary adj2 (spread or attack* or transmission*)).ti,ab.
(case adj (finding or detect* or identif*)).ti,ab.
or/40-50
Isolation.ti.
isolat*.ti,ab. and (Cross Infection/ or Hospital Infection/ or exp Disease Transmission/ or Infection control/ or
Import disease/)
(Isolat* and (cross infection or nosocomial* or infection control or outbreak* or hospital acquired or healthcare
associated or health care associated or hospital associated or communicable)).ti,ab.
(isolat* and (import* adj4 (case or cases or virus or disease))).ti,ab.
(!!isolator* or isolation or isolating or isolate or isolated or segregat* or containment) adj3 (patient* or ward* or
unit* or room* or precaution* or pre-caution* or preemptive or pre-emptive or contact* or practice* or measure
or measures or facility or facilities or period* or strateg*)).ti,ab.
(quarantin* or quarantain* or cohorting or cohort nursing or superisolation or isolette* or droplet precaution* or
reverse isolation).ti,ab.
or/52-57
Vaccination/ or Measles vaccination/ or Revaccination/ or Measles vaccine/ or exp Immunoglobulin/ or Mass
immunization/
(vaccinat* or immuniz* or immunis* or immunoglobulin* or immune globulin* or vaccine* or inoculat*).ti,ab.
59 or 60
Import disease/ or Epidemic/ or Pandemic/
(outbreak* or importation* or secondary spread or secondary transmission*).ti,ab.
((epidemic* or pandemic*) adj4 measle*).ti,ab.
62 or 63 or 64
((target* or outbreak*) adj3 (response* or campaign* or stratag*)).ti,ab.
((target* or outbreak*) adj (vaccinat* or immuniz* or immunis* or inoculat*)).ti,ab.
66 or 67
Public Health Interventions to Reduce Secondary Spread of Measles

(3 and (15 or 22)) or (3 and 25 and 29) or (3 and 32)
(39 and (51 or 58)) or (39 and 61 and 65) or (39 and 68)
69 use pmez
70 use cctr
71 69 use oemezd
72 73 not conference abstract.pt.
73 71 or 72 or 74
74 limit 75 to yr="1994 -Current"
75 limit 76 to (english or french)
76 remove duplicates from 77

OTHER DATABASES

PubMed
Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

GREY LITERATURE

Dates for Search: August 18 – To be determined
Keywords: Measles, rubeola, outbreak, outbreak response
Limits: Publication years 1994-present

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Databases (free)
- Internet Search