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Public Health Interventions to Reduce the Secondary Spread of Measles

Supporting Informed Decisions

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Public Health Interventions to Reduce the Secondary Spread of Measles

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ACRONYMS AND ABBREVIATIONS

CI	confidence interval
Ig	immunoglobulin
MMR	measles-mumps-rubella [vaccine]
NA	not applicable
NHIG	normal human immunoglobulin
NR	not reported
OR	odds ratio
PAHO	Pan American Health Organization
PEP	post-exposure prophylaxis
RCT	randomized controlled trial
RR	relative risk
SAR	secondary attack rate
VE	vaccine effectiveness

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EXECUTIVE SUMMARY

Context and Policy Issues

Measles is a highly communicable infectious disease, with 90% of susceptible contacts (those who have not had measles or are unimmunized) becoming infected after exposure to a person with measles. Serious complications include blindness, encephalitis, and pneumonia. Treatment is limited; however, measles is largely preventable through immunization, with efficacy approaching 100% after two doses of measles-containing vaccine. Although vaccination programs have eliminated endemic measles (i.e., measles circulating within the country) in Canada, outbreaks occur due to foreign travel and pools of unimmunized Canadians. Public health interventions to reduce the secondary spread of measles are vaccination of susceptible contacts; human immunoglobulin (Ig) for susceptible contacts; quarantine of susceptible contacts; isolation of active measles cases; and special vaccination clinics or activities during outbreaks to increase population immunization coverage. The objective of this study is to inform the development of a Canadian public health intervention strategy by systematically reviewing the clinical evidence on the effectiveness of these five public health interventions in reducing the secondary spread of measles during an outbreak in a population similar to Canada that has achieved elimination of endemic 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

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, Embase, Cochrane Central via Ovid, and PubMed. The Cochrane Library (2014, Issue 9) and the University of York Centre for Reviews and Dissemination (CRD) databases were also searched. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is). No methodological filters were applied to limit retrieval by publication type. The search was limited to English or French language documents published between January 1, 1994, and September 25, 2014. Regular alerts were established to update the search until project completion.

Eligibility criteria established a priori included RCTs and non-randomized studies with a no-treatment control group, involving the administration of an intervention within the scope of the research questions to people of any age, living in countries with vaccination rates, programs, and socioeconomic status similar to Canada. Restricting the evidence to countries with measles elimination status was initially deemed to be the most relevant to the current Canadian context. However, scoping activities revealed that restricting the review to evidence published solely by countries with measles elimination status (i.e., Region of the Americas) was limiting, and therefore the scope of included countries was expanded a priori to include the United States, 22 countries in Western Europe, and Australia and New Zealand. Publication year limits were 1994 to present for Pan American Health Organization (PAHO) countries, 1999 to present for European Region, and 2005 to present for the Western Pacific Region, representing the years when these regions committed to regional measles elimination goals. These years were selected as

proxy indicators of the likely public health effort to respond to measles importations or outbreaks. Before this time, public health responses may not have been as intensive as in the elimination or post-elimination periods; thus, studies from the pre-elimination periods were excluded.

Two reviewers independently screened the titles and abstracts of retrieved citations and ordered the full text of articles that met the inclusion criteria. The reviewers subsequently independently reviewed the full text of the selected articles, applied the selection criteria, and identified eligible studies. Disagreements were resolved through discussion until consensus was reached. Data were extracted independently by two reviewers and any disagreements were resolved through discussion with a CADTH methodology expert. One reviewer used the validated Downs and Black checklist as a guide to assess study quality based on criteria relating to quality of reporting, external validity, and risk of bias. A second reviewer verified the assessments. A narrative synthesis of results of included studies was conducted.

Summary of Findings

Seven articles were selected as being relevant to the research questions (six retrospective cohort studies and one retrospective case-control study), with outbreaks spanning 1990 to 2007 and reported from Australia, Canada, Spain, Switzerland, and the United Kingdom (UK).

- With respect to vaccinating susceptible contacts with measles-containing vaccine, five studies met the inclusion criteria. Four studies showed a benefit from the intervention, although only two reached statistical significance; one study showed no benefit from the intervention.
- With respect to administration of Ig to susceptible contacts, one study was reviewed that showed a reduced risk of contracting measles for those who received Ig as compared with those who did not, although the result was not statistically significant.
- With respect to quarantine of susceptible contacts, the one identified study showed a statistically significant reduction in the relative risk versus no quarantine.
- No studies reported on subsequent disease spread for isolation of measles cases.
- One study from northern Canada reported on a special program launched to immunize infants aged six to 11 months during a local outbreak, in which a statistically significant reduced risk of contracting measles was observed for the infants who were immunized as compared with those who were not immunized.

Conclusions and Implications for Decision- or Policy-Making

Although a small number of studies were included for each research question, together evidence from seven observational studies offers support for inclusion of four of the five interventions in a public health intervention strategy for reducing the secondary spread of measles during an outbreak. These interventions include immunization of susceptible contacts with measles-containing vaccine (five studies), Ig administration to susceptible contacts (one study), quarantine of susceptible contacts (one study), and a special within-outbreak program that aimed to immunize all infants aged six to 11 months (one study). Although isolation of measles cases is currently recommended, no literature on this topic was located that met eligibility criteria for this review. The strongest available evidence concerns administration of measles-containing vaccine, with four of five included studies demonstrating a benefit (two of statistical significance and two showing a non-significant positive trend) and the fifth small study (n = 6) demonstrating no benefit. All included studies were limited by a number of issues related to external and internal validity, such as location in different countries with different health systems, resources, and staff training; variations in methods of case confirmation; and delays in diagnosis, which may cause the window for prophylactic treatment to be exceeded.

1. CONTEXT AND POLICY ISSUES

Measles is a highly communicable infectious disease that is spread through droplets from the nose or throat (e.g., by coughing or sneezing).[1,2] Symptoms include fever, runny nose, cough, conjunctivitis, drowsiness, irritability, and a maculopapular (red and 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.[3] Cases are infectious from one day before the beginning of the prodromal period (several days when symptoms are non-specific, before the disease is evident) to four days after rash onset, and more than 90% of susceptible contacts will become infected after exposure to a case of measles.[4]

Susceptible contacts are people (including infants) who have not had measles disease or who have not been successfully vaccinated; in Canada, adults born before 1970 are considered to have acquired natural immunity to measles.[4] Unvaccinated children and young adults are at a higher risk of developing measles and they place vulnerable groups, such as infants and persons with contraindications to immunization, at risk.[5] (Definitions are included in Appendix 1.)

Complications are rare but can be serious, including blindness, encephalitis, and pneumonia.[3] In developed countries, complications occur in about 10% of measles cases and death is estimated to occur in one to two of every 1,000 cases.[4] Globally, measles is a leading cause of death among young children; according to the World Health Organization, 22,000 children died worldwide as a result of measles in 2012.[6] There are limited treatments beyond supportive care; however, measles is largely preventable through immunization.[3] The efficacy of a single dose of measles vaccine given at 12 or 15 months of age is estimated to be 85% to 95%, and it is almost 100% with a second dose.[4]

Routine publicly funded measles vaccine programs were implemented in Canada in the early 1970s. By 1983, rubella and mumps were added to the routine schedules, with one dose of the combined measles-mumps-rubella (MMR) vaccine now given to infants at age 12 to 15 months.[4] In the late 1990s, provinces and territories added a second dose of MMR to the routine schedule, with the second one now given at 18 months up to school entry age.[4]

Currently, the most effective preventive measure is reported to be two doses of MMR vaccination, with vaccine uptake in the population of at least 95% to ensure adequate herd immunity and protection of unvaccinated individuals.[7] Based on national surveys, Canada is believed to have achieved immunization rates of this magnitude, although a national vaccine registry is not in place.[6] A new combined multivalent vaccine (measles-mumps-rubella-varicella vaccine [MMRV]) has become available for children aged 12 months to 12 years.[4]

Endemic measles is defined as the existence of any continuous indigenous chain of transmission of measles virus that persists for more than one year in any defined geographic area.[8] Although vaccination programs have eliminated endemic measles in Canada, importations and outbreaks continue to occur due to travel to countries with disease activity, and susceptible individuals and communities who are unimmunized or under-immunized.[6] From 1998 to 2013, 1,429 confirmed measles cases were reported in Canada, with a median of 21.5 cases per year (range: 6 to 752).[4] Five public health interventions used to reduce the secondary spread of measles are:[9]

- Vaccination of susceptible contacts within 72 hours of exposure
- Administration of human immunoglobulin (Ig) to susceptible contacts within six days of exposure
- Quarantine of susceptible contacts (potential case is separated from non-cases)
- Isolation of those infected with measles
- Vaccination clinics or activities above and beyond routine vaccination services to increase population immunization coverage (for example, extended hours of immunization services, mobile units, and vaccination clinics that target a specific

population based on age, immunization status, or geographic location).

The order of intervention follows a staged approach.[4,9] Typically, measles-containing vaccine is the first choice of intervention for susceptible contacts (within three days of exposure),[‡] followed by Ig (after three days but within six days following exposure for those who would have been vaccine candidates, and also immediately after exposure for those who are not vaccine candidates, such as susceptible pregnant women, susceptible immunocompromised people, and children younger than six months of age), and quarantine for susceptible contacts who refuse or cannot receive vaccine or Ig. Isolation is applied to measles cases only, and other targeted vaccination activities may be applied to specific populations, depending on the outbreak and situation. Public health interventions are applied through tracing of contacts and identifying those susceptible to measles and who are therefore candidates for additional management (although swift control efforts by public health agencies are time- and resource-intensive, and costly).[5]

Policy related to the public health interventions to reduce the secondary spread of measles is well established in countries such as Canada, although in some cases, the evidence underlying the policy statements is unclear. The objective of this study is to inform the development of a Canadian public health intervention strategy by systematically reviewing the clinical evidence on the effectiveness of public health interventions in reducing the secondary spread of measles during an outbreak in a population similar to Canada, which has achieved elimination of endemic measles.

[‡]Determining the timing of exposure to a measles case can be a challenge and is often not known or reported. Contact may involve a single discrete exposure or multiple exposures over several days, particularly during the prodromal stage of the disease; e.g., for a student in a classroom who remains at school or daycare while infectious.

2. RESEARCH QUESTIONS

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

3. KEY FINDINGS

Seven studies were identified that addressed the five research questions. Four public health interventions to prevent secondary spread of measles were supported by weak evidence, including immunization of susceptible contacts with measles-containing vaccine (five studies), Ig administration to susceptible contacts (one study), quarantine of susceptible contacts (one study), and a special within-outbreak program that aimed to immunize all infants aged six to 11 months (one study). Although isolation of measles cases is often recommended by public health authorities, no relevant literature meeting the eligibility criteria was identified for this question. The strongest available evidence relates to administration of measles-containing vaccine, with four of five included studies demonstrating a potential benefit (two reaching statistical significance) and the fifth small study (n = 6) demonstrating no benefit. All included studies were limited by a number of issues related to external and internal validity, such as location in different countries with different health systems, resources, and staff training; lack of laboratory confirmation in many cases; and delays in diagnosis and confirmation,

meaning the window for prophylactic treatment was exceeded.

4. METHODS

4.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was 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 consisted of controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts were outbreak response methods (vaccine delivery, immunoglobulin delivery, quarantine, isolation, and targeted vaccination activities) and measles. No methodological filters were applied to limit retrieval by publication type. The search was limited to English or French language documents published between January 1, 1994, and September 25, 2014. Biweekly alerts were established to update the search until project completion. Conference abstracts were excluded from the search results. See Appendix 2 for detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching sources identified through relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

4.2 Selection Criteria and Methods

Selection criteria established a priori included RCTs and non-randomized studies with a no-treatment control group, involving the administration of an intervention within the scope of the research questions to people of any age, living in countries with socioeconomic status and vaccination rates and programs similar to Canada (Table 1). Restricting the evidence to countries with measles elimination status was initially deemed to be the most relevant to the current Canadian context. However, scoping activities revealed that restricting the review to evidence published solely by countries with measles elimination status (i.e., Region of the Americas) was too limiting, and therefore the scope of included countries was expanded a priori to include the United States, 22 countries in Western Europe, Australia, and New Zealand. Publication year limits were 1994 to present for Pan American Health Organization (PAHO) countries, 1999 to present for European Region, and 2005 to present for the Western Pacific Region, representing the years when these regions committed to regional measles elimination goals. These years were selected as proxy indicators of the likely public health effort to respond to measles importations or outbreaks. Before this time, public health responses may not have been as intensive as in the elimination or post-elimination periods; thus, studies from the pre-elimination periods were excluded.

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, ordered the full text of articles that met those criteria. The reviewers then independently reviewed the full text of the selected articles, applied the selection criteria to them, and compared the independently chosen included and excluded studies. Disagreements were resolved through discussion until consensus was reached.

Table 1: Literature Selection Criteria	
Populations	• All ages • Countries or WHO Regions with public health and outbreak response guidelines similar to Canada:[a] (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, or clinical case of measles (outbreak, importation, exposure on a conveyance) • Question 4: Person with confirmed, probable, or clinical measles • Question 5: Population targeted due to a relevant factor such as age, immunization status, or geographic location
Interventions	Question 1: Vaccine delivery (all forms and schedules of vaccine) Question 2: Ig delivery (all forms and schedules) 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 for intervention (includes non-contacts)
Comparators	Question 1: No vaccine delivery Question 2: No Ig delivery Questions 3 and 4: No isolation or quarantine strategies Question 5: No vaccination activities; i.e., regular vaccination activities that would occur in the absence of an outbreak
Outcomes	Incidence of confirmed measles cases, incidence 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	RCTs and non-randomized studies with a comparator group

Ig = immunoglobulin; PAHO = Pan American Health Organization; RCT = randomized controlled trial; WHO = World Health Organization.
[a] Publication year limits: 1994 for PAHO countries, 1999 for European Region, 2005 for Western Pacific Region. (These are the years in which the regions committed to regional measles elimination goals — selected as proxy indicators of the likely public health efforts to respond to measles importations or outbreaks.)

4.3 Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to the publication year limits (Table 1), or if they were duplicate publications of the same study. In particular, the following were considered out of scope:

Population: Susceptible individuals in countries with poor vaccination rates that do not have similar public health systems or guidelines in place to respond to measles outbreak.

Interventions: Interventions to treat measles (e.g., vitamin A injections), different surveillance activities, and different vaccinations or schedules of vaccinations.

Comparators:

- Question 1: (a) Effectiveness across different vaccines, or (b) different definitions of susceptible contacts
- Question 2: Effectiveness across different definitions of susceptible contacts
- Questions 3 and 4: (a) Effectiveness across different quarantine or isolation strategies, including different timing of quarantine or isolation strategies, or (b) different definitions of susceptible contacts
- Question 5: (a) Effectiveness across different clinical variables, or (b) different definitions of susceptible contacts.

Outcomes: Effectiveness of vaccines in a routine scenario (no measles outbreak; primary prevention); effectiveness of Ig provided in a routine scenario; adverse events of routine, scheduled vaccinations of the population; morbidity or adverse effects of measles other

than those specified in the selection criteria; and adverse events from any included intervention.

Study types: Observational studies without a comparator group, ecological or modelling studies, and case reports.

4.4 Data Extraction Strategy

Extracted data adhered to the criteria identified in Table 1. Data were extracted independently by two reviewers and any disagreements resolved through discussion with a CADTH scientific advisor.

4.5 Critical Appraisal of Individual Studies

One reviewer used the validated Downs and Black checklist[10] to assess study quality based on criteria relating to quality of reporting, external validity, and risk of bias. A second reviewer verified the assessments and disagreements were resolved through discussion until consensus was reached. Numeric scores were not calculated; instead, a narrative and tabular description of the strengths and limitations of each included study was presented.

4.6 Subgroup Analyses

Subgroup analyses were planned, if data were sufficient, including:

- Effectiveness of measles-containing vaccine administered to susceptible contacts during the outbreak, based on the number of previously administered (i.e., pre-outbreak) vaccine doses (0, 1)
- Effectiveness of vaccine and Ig delivery within versus outside the recommended time frame
- Effectiveness of different concentrations of Ig
- Hospitalizations and deaths in high-risk (see Appendix 1) versus other contacts.

5. RESULTS

5.1 Quantity of Research Available

The process of study selection is outlined in the PRISMA flowchart (Appendix 3). The literature search yielded 3,218 citations. Upon screening titles and abstracts, 3,097 citations were excluded and 121 potentially relevant articles were retrieved for full-text review. No potentially relevant reports were retrieved from grey literature or handsearching and three additional potentially relevant references were identified via literature alerts.[11-13] Of the 124 potentially relevant reports, seven were selected as being relevant to the research questions (Appendix 4) and 117 were excluded (Appendix 5). The seven included studies addressed the research questions about effectiveness as follows:

- Measles vaccine for susceptible measles contacts = five studies
- Ig for susceptible measles contacts = one study (this study also addressed Question 1)
- Quarantine of susceptible measles contacts = one study
- Isolation of communicable measles cases = zero studies
- Targeted measles vaccination activities during an outbreak= one study.

Articles not eligible for this review are listed in Appendix 5, some of which might be of interest despite their lack of a comparison group (Section C in Appendix 5).

5.2 Study Characteristics

The studies are described according to the research questions they addressed. Individual study detail is presented in data tables in Appendix 6.

Measles vaccine for susceptible measles contacts

Five studies addressed this strategy: two from Canada,[14,15] one from Australia,[16] one from Spain,[7] and one from the UK.[17] The span of publication dates was 1994 to 2011. Although two outbreaks were recent (2006/07),[7,16] two of the outbreaks studied were from the early- to

mid-1990s (1990 and 1995; both in Ontario, Canada)[14,15] before the two-dose MMR strategy was in place. Four studies focused on children or adolescents through institutional (school or child care) exposure.[7,14,15,17] The fifth[16] covered the general population with a contact being defined as a person who was in the same room as the measles case during the infectious period or in the same room for up to two hours after the measles case was there.

The strategies for management of susceptible contacts varied:

- In the earliest Canadian study (1990 to prior to the current two-dose regimen),[15] if there were two or more measles cases at a school, a second dose of measles-containing vaccine was offered to students during the outbreak if they had received a first measles vaccine before 1980, due to an observed higher rate of vaccine failure in people vaccinated before this date. While not recommended at the time, the parents of some children who were vaccinated before 1980 also sought revaccination and were included in the analysis. Excluded from the analysis were students who had never received measles vaccine; had received more than one dose of measles vaccine before September 1, 1990, the start of the outbreak; or did not attend school in the community.
- In the other Canadian study,[14] measles vaccine was offered to susceptible contacts (defined as those born after 1956 without previous measles vaccine, or measles confirmed via laboratory testing, or previous measles vaccine before first birthday with no previous measles).
- In a UK study,[17] an unimmunized 17-month-old index case was in close contact at a nursery with six other children around the same age, all unimmunized, during the entire period that the index case had cold-like nasal symptoms. The index case was diagnosed with measles after three days of symptoms (laboratory-confirmed), and the parents of the six other children were advised to have their children immunized immediately. Four were compliant.
- In the Australian study,[16] MMR vaccine was offered to susceptible contacts (defined as those with inadequate immunity) within three days of exposure or Ig within seven days of exposure. Inadequate immunity was defined according to Australian guidelines as infants aged six to 12 months; children aged one to four years who had not received any doses of MMR; and children older than four years and adults born during or after 1966 who had not received two doses of MMR.
- In the most recent study in Spain,[7] MMR vaccine was offered to susceptible contacts (defined as those with no previous vaccine or measles), ideally within three days of exposure (although a number of susceptible contacts were treated several days later).

Current Canadian guidelines[9] for managing susceptible contacts recommend MMR immunization for those older than six months who are within 72 hours of exposure, and Ig for those exposed in a window longer than 72 hours but shorter than six days, plus those who are immunocompromised, pregnant or younger than six months. For susceptible contacts who refuse or cannot receive MMR vaccine or Ig, the guidelines suggest that these people "*may be excluded from child care facilities, schools, and post-secondary educational institutions at the discretion of the Medical Officer of Health; and may be required to self-isolate from work places, or other group settings, including travel. If exclusions occur, the period of exclusion should extend from five days after the first exposure and up to 21 days after the last exposure, or until the individual is (a) adequately immunized (having had documentation of at least one recent dose of a measles-containing vaccine), or (b) demonstrates serological confirmation of immunity or has received Ig, if eligible*"[9] (pg. 14). The guidelines[9] also recommend that measles cases should be advised to self-isolate away from non-household contacts for four days after the appearance of the rash.

Four studies were retrospective cohort studies, while the earliest study[15] was a retrospective matched (1:2) case-control. In the case-control

study, controls were selected from homeroom class lists via random number allocation with the following exclusions applying: had never received measles vaccine; had received more than one dose of measles vaccine before September 1, 1990; had a documented history of measles; had signs and symptoms that met the measles definition during the outbreak; did not attend school in the community; and were absent from school during the entire infectious period of the matched case patient.

All studies reported the incidence of measles among treated and untreated individuals. Untreated individuals were those who refused treatment, were not contacted within the treatment window, or could not be contacted. Confirmed measles cases were generally defined as those meeting the laboratory-confirmed definition and/or those meeting the clinical definition with an epidemiological link to a laboratory-confirmed case; two studies[7,16] did not report the proportions meeting each definition, whereas the other three[14,15,17] specifically reported the proportions of laboratory-confirmed cases as 16%,[14] 48%,[15] and 100%.[17]

The four cohort studies allowed for calculation of the relative risk of contracting the disease between treated and untreated groups, whereas the matched case-control study allowed for calculation of the odds of vaccine recipients contracting measles as compared with people who did not receive the vaccine.

Immunoglobulin for susceptible measles contacts

One retrospective cohort study addressed this strategy: a 2009 report from Australia that also examined the strategy of vaccinating susceptible measles contacts, as described above.[16] The retrospective cohort study assessed the effectiveness of MMR vaccine within three days of exposure or Ig within seven days of exposure as post-exposure prophylaxis (PEP), as compared with no treatment, during an outbreak in New South Wales. The study therefore contributed data to two research questions. The dose and type of Ig administered were not reported, although reference was made to an Australian guideline recommended dose of 2.0 mL/kg. The outcome of interest was measles occurrence, defined as either laboratory-confirmed or clinical (fever and/or cough and/or coryza and/or conjunctivitis and maculopapular rash) with an epidemiological link to a laboratory-confirmed case. Contacts identified as susceptible were offered one of these PEP treatments, depending on age and time since exposure. Susceptible contacts who did not receive a PEP treatment, either because they refused (16.8%) or could not be identified within the seven-day treatment window and thus were not offered the intervention (35.3%), were included in a control group.

Quarantine of susceptible measles contacts

Quarantine was addressed in a 2013 retrospective cohort study from Geneva Canton in Switzerland.[18] The study assessed the effectiveness of quarantine on measles transmission during an eight-month local outbreak, as compared with no quarantine. Siblings or classmates of measles cases who were unvaccinated or non-immune (defined as people born after 1963 without vaccination or Ig, or proven history of disease) were recommended quarantine for 18 days after last contact with a case, or the appearance of the measles case's rash. Those individuals who did not comply with quarantine formed the control group. The outcome of interest was measles cases defined as laboratory-confirmed (63%); clinical and epidemiologically linked (26%); probable (7%); and possible (4%). For this study, total incidence of measles cases was calculated as the combination of laboratory-confirmed, clinical and epidemiologically linked, and probable measles cases; possible cases were excluded from the analysis.

Isolation of communicable measles cases

No studies were located that met the inclusion criteria and examined the effectiveness of this strategy.

Targeted measles vaccination activities during an outbreak

One retrospective cohort study addressed a special vaccination initiative[19] in which infants aged six to 11 months were immunized during a local measles outbreak in 1991. A single index case in an adult led to 15 subsequent local measles cases. The study report focused on provision of monovalent measles vaccine for the target group of infants, all of whom were unimmunized and presumed to be susceptible. In total, 81 infants aged six to 11 months (mean age 8.5 months) were identified as susceptible, although only 56 (69%) were available for immunization in the communities, as 23 were not present during the immunization drive. These 23 infants served as the untreated control group for the analysis.

5.3 Critical Appraisal of Individual Studies

Of the seven included studies, one was designed as a retrospective matched case-control study.[15] The others were retrospective cohort studies that included groups of susceptible people who did and did not receive an intervention, thus allowing for comparisons. While the inclusion of a control group increases the strength of the conclusions, these observational studies suffer from a risk of bias due to uncontrolled confounders, the characteristics of which were not reported or adjusted for within most studies.

With respect to quality of reporting, most details required to conduct a critical appraisal were reported, although reporting was often limited. For example, one study[17] was only described in a letter to a journal, authored by local public health personnel, with three paragraphs dedicated to study details. This meant that some details were omitted from the report, including information about case confirmation and data collection. Patient characteristics were poorly reported in most studies. The specific vaccines used and types and dosing procedures for Ig were not reported in any of the studies. In some studies, the time from exposure to intervention (measles-containing vaccine or Ig) was likewise not reported.

One vaccination study[7] assessed the outcomes when susceptible contacts received vaccine within versus outside the recommended three-day window. In this study, 75 contacts were susceptible and 54 (72%) were immunized, but only 17 of the 54 (32%) received vaccine within the three-day treatment window and the median time to intervention was five days (range one to 12 days). Details of outcomes based on day of post-exposure immunization are contained in subgroup analysis. Another vaccination study[17] reported that four of six susceptible infants who were vaccinated received the injections on day 4 of the illness for the index case, although details were not reported regarding the time from exposure to vaccination. The three remaining vaccination studies did not provide data on time to intervention.[14-16] Likewise, no data on time to intervention were provided by the study on Ig in which 183 susceptible contacts received this intervention.[16]

With respect to external validity of the results, due to inadequate reporting of patient and population characteristics, it was often not clear whether the populations studied were representative of the larger populations from which they were drawn and to whom study results are intended to apply. While many of the studies were population-based, no comparisons were reported between sample and population characteristics. This means that in some cases, the samples may not be representative of the larger populations.

With respect to internal validity, there are several potential concerns. For example, in some cases it was unclear whether measles cases, treated contacts, and untreated contacts were comparable with regard to important determinants, raising the potential for confounding: aside from age ranges, demographics of cases and controls were generally not described. In each of the included studies, the control group comprised individuals who refused the intervention or could not be contacted within an appropriate time frame to be offered the intervention. Due to a lack of reporting of sample characteristics, it was unclear whether people who received the intervention were different in any meaningful

way from people who did not. It is therefore possible that the reported results are biased, although without reporting of patient characteristics, it is unclear in what direction, if any. It was also unclear in some cases whether there was valid and reliable measurement of exposure and outcomes (i.e., incidence of measles) for the various groups studied. Furthermore, in one study, the control group comprised infants who were out of the community during the vaccination drive, some of whom were absent during the outbreak as well and therefore had a reduced risk of measles exposure as compared with those who remained in the community during the outbreak and vaccination drive. No RCTs were identified through the literature search, as RCTs with a no-treatment control group in the context of a measles outbreak are unlikely for ethical concerns and there are difficulties running a controlled trial in this scenario. Patients (or their carers) self-selected in terms of proceeding to the recommended course of action (vaccination, Ig, or quarantine) as treatment was not mandatory.

Reported results therefore better reflect real-world effectiveness of these public health interventions, but not efficacy. Similarly, in some cases, delays in diagnosis and confirmation meant the window for prophylactic treatment was exceeded, so a number of susceptible contacts were not offered immunization or Ig. Also, in several studies, follow-up was not adequate to ensure additional cases did not present. For example, in one study[7] it was unclear how long the susceptible contacts were checked for measles once the index cases had been identified; in another,[16] follow-up ended May 31, yet two measles cases were reported the week of May 24, meaning further cases were still possible.

Aside from one study, sample size calculations were not reported; therefore, it was not clear whether most samples were large enough to detect meaningful differences. The exception was the case-control study, in which a sample size of at least 24 was required and observed.[15] Further details regarding critical appraisal are contained in the data tables in Appendix 7.

5.4 Data Analyses and Synthesis

Additional detail is contained in the tables in Appendix 8. Meta-analysis and subgroup analyses were not possible due to the variability in study characteristics for question 1, and because only one study was located for each of the other three research questions.

Measles vaccine for susceptible measles contacts

The results for the five studies that addressed this question are presented in Table 2. The most recent study from Spain[7] showed a benefit to PEP with MMR, with a relative risk (RR) of 0.4 (95% confidence interval [CI], 0.2 to 0.6] for those given the vaccine versus those not receiving vaccine. This study also analyzed the results when the vaccine was provided within three days of exposure (the currently recommended treatment window), which also gave a statistically significant result with a relative risk of 0.14 (95% CI, 0.02 to 0.98) for the 17 of 54 children (32%) in this group. Results for vaccination of the 37 of 54 children (68%) treated beyond the recommended three-day treatment window are presented in a subgroup analysis. The results were also statistically significant in the earliest study from Ontario[15] with an odds ratio of 0.23 (95% CI, 0.11 to 0.50). The results of the study from Australia[16] and the second Canadian study,[14] while in favour of measles vaccination, were not statistically significant. In contrast, in the small UK study,[17] there were six nursery school contacts who were all considered susceptible. Four of the six children were immunized the day that the index case was diagnosed (day 4 of illness for the index case) but all of the children developed measles. There was therefore no evidence of a difference in the relative risk of measles in the vaccinated and unvaccinated children (RR 1.0).

Table 2: Results for Studies Assessing Effectiveness of Measles Vaccine for PEP					
	Barrabeig et al., 2011[7]	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
Measles in contacts who received vaccine, n/N (%)	12/54 (22.2)	0/82 (0)	4/4 (100)	2/33 (6.1)	9 cases were revaccinated during the outbreak[c]
Measles in contacts who did not receive vaccine, n/N (%)	13/21 (61.9)	13/288 patients (4.5) did not receive PEP (Ig or MMR)	2 / 2 (100)	83/986 (8.4)	78 cases were not revaccinated during the outbreak[c]
RR or OR (95% CI) of developing measles for contacts who received vaccine	RR 0.4 (0.2 to 0.6)	RR 0.13 (0.01 to 2.15)	RR 1.0[a] (CI not calculated due to small sample)	RR 0.72 (0.18 to 2.8)[a]	OR 0.23 (0.11 to 0.50)[b]
RR (95% CI) of developing measles for contacts who received vaccine within 3 days of exposure	0.14 (0.02 to 0.98)[a]	NA	NA	NA	NA

CI = confidence interval; Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; NA = not applicable; NR = not reported; OR = odds ratio; PEP = post-exposure prophylaxis; RR = relative risk.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php) (*Note: for zeros, 0.5 is added to calculate the RR and CI).*
[b] Calculated by CADTH (OR calculator) (http://www.medcalc.org/calc/odds_ratio.php).
[c] In this case-control study, by definition, controls did not contract measles.

Immunoglobulin for susceptible measles contacts

The Australian study that addressed this strategy[16] reported on the results of offering Ig to susceptible contacts from days 4 to 7 post-exposure (i.e., those who missed the three-day post-exposure window required for MMR vaccination) to achieve the recommended Ig seven-day treatment window in Australia. As shown in Table 3, the analysis indicated a reduced risk for those administered Ig, although the result was not statistically significant with a relative risk of 0.24 (95% CI, 0.06 to 1.06). It was unclear whether contacts who developed measles despite Ig use experienced a milder or different presentation.

Table 3: Results for Study Assessing Effectiveness of Immunoglobulin for Measles Contacts	
	Sheppeard et al., 2009[16]
Susceptible contacts who received Ig, n/N (%)	183/553 (33)
Susceptible contacts who did not received Ig, n/N (%)	288/553 (52)
Incidence of measles in contacts who received Ig, n/N (%)	2/183 (1.1)
Incidence of measles in contacts who did not receive PEP (Ig or MMR), n/N (%)	13/288 (4.5)
Ig effectiveness, % (95% CI)	75.8 (0 to 94)
RR[a] of developing measles for contacts who received Ig (95% CI)	0.24 (0.06 to 1.06)

CI = confidence interval; Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; PEP = post-exposure prophylaxis; RR = relative risk.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php).

Quarantine of susceptible measles contacts

The Swiss study[18] that analyzed the effectiveness of quarantine for susceptible contacts showed a 74% reduction in the secondary attack rate versus no quarantine. Of 73 susceptible contacts who were quarantined, 50 developed measles and these caused six secondary cases (all among household contacts). In contrast, 173 non-quarantined cases led to 81 secondary cases of measles (48 in household members and 33 in the community). The reported relative risk was significant at 0.26 (95% CI, 0.06 to 0.56) (Table 4).

Table 4: Results for Study Assessing Effectiveness of Quarantine for Measles Contacts	
	Delaporte et al., 2013[18]
Susceptible contacts quarantined, n/N (%)	73/NR (NR)
Susceptible contacts who were not quarantined, n/N (%)	NR
Incidence of measles	
• In contacts who were quarantined, n/N (%)	50/73 (69)
• In contacts who were not quarantined, n/N (%)	173/NR (NR)
○ Cases arising from measles cases who were quarantined, n/N (%)	6/50 (12): all household members — none in the community)
○ Cases arising from measles cases who were not quarantined, n/N (%)	81/173 (47): 48 (59) household members — 33 (41) in the community
SAR reduction	74%
RR (95% CI) of developing measles for contacts who were quarantined	0.26 (0.06 to 0.56)
RR (95% CI) for household members	0.43 (0.09 to 1.00)
RR (95% CI) for community members	0.05 (0.00 to 0.69)

CI = confidence interval; NR = not reported; RR = relative risk; SAR = secondary attack rate.

Isolation of communicable measles cases

No studies were identified that met the inclusion criteria and examined the effectiveness of this strategy.

Targeted measles vaccination activities during an outbreak

Eighty-one infants aged six to 11 months were identified as susceptible in eight northern Canadian Inuit communities,[19] although only 56 (69%) were available for immunization. The remaining 23 infants were out of the community during the vaccination drive and some were absent during the outbreak as well (proportion not reported) and therefore had a reduced risk of measles exposure. The natural division of the infant population allowed for a comparison of secondary measles attack rate between the immunized and non-immunized groups. Table 5 shows the benefit of targeted immunization of unimmunized infants aged six to 11 months in this situation, with a relative risk for this group of 0.27 (95% CI, 0.11 to 0.68), most pronounced for the infants aged nine to 11 months (RR 0.21; 95% CI, 0.04 to 0.98).

Table 5: Results for Study Assessing Effectiveness of a Targeted Program for Measles Contacts in Children Aged 6 to 11 Months	
	De Serres et al., 1996[19]
Susceptible contacts who received vaccine, n/N (%)	56/81 (69)
Ages 6 to 8 months	27/39 (69)
Ages 9 to 11 months	29/42 (69)
Susceptible contacts who did not receive vaccine, n/N (%)	23/81 (28)
Susceptible contacts who received Ig, n/N (%) (not included in authors' analysis)	2/81 (3)
Incidence of measles (excludes the 2 infants who received Ig)	
• Total measles cases, n/N (%)	15/79 (19)
• Measles in contacts who received vaccine, n/N (%)	6/56 (11)
○ Ages 6 to 8 months	4/27 (15)
○ Ages 9 to 11 months	2/29 (7)
• Measles in contacts who did not receive vaccine, n/N (%)	9/23 (39)
○ Ages 6 to 8 months	5/11 (45)
○ Ages 9 to 11 months	4/12 (33)
RR (95% CI) [a] of developing measles for contacts who received vaccine	0.27 (0.11 to 0.68)
RR (95% CI) ages 6 to 8 months [a]	0.33 (0.11 to 0.99)
RR (95% CI) ages 9 to 11 months [a]	0.21 (0.04 to 0.98)
RR reduction, measured as VE[b] % (95% CI)	73 (32 to 89)

CI = confidence interval; Ig = immunoglobulin; NR = not reported; RR = relative risk; VE = vaccine effectiveness.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php).
[b] VE = [(attack rate unvaccinated – attack rate vaccinated) / attack rate unvaccinated] x 100; CI calculated using a Taylor series.

Subgroup analyses

Two of the four proposed subgroup analyses were possible. Due to lack of reporting of results according to the required characteristics, the remaining proposed analyses were not possible.

a) **Effectiveness of vaccine or Ig for susceptible contacts based on the number of prior doses of measles-containing vaccine:** The 1996 Canadian study[14] included data on the number of susceptible contacts contracting measles based on prior immunization status. For those who were unimmunized (zero doses) before the outbreak, the relative risk for contracting measles in those who received PEP was 0.49 (95% C1, 0.02 to 11.7), and for those who were under-immunized (one previous dose) who received PEP, the relative risk was 3.3 (95% CI, 1.0 to 10.8). The study results showed that two doses of vaccine given before the outbreak conferred significant protection with a relative risk of failure (lack of protection against measles) after one dose versus two doses of 5.0 (95% CI, 1.3 to 20.2). The Australian study[16] assessed the effectiveness of Ig for PEP but, although susceptible contacts included children older than four years and adults born during or after 1966 who had not received two doses of MMR, there was no analysis of response to Ig administration depending on whether zero or one dose had been previously provided.

b) **Effectiveness of vaccine and immunoglobulin delivery within — versus outside — the recommended time frame:** The effectiveness of vaccine delivery within — versus outside — the recommended time frame (three days) was explored by the authors of the Spanish study.[7] They reported that when vaccine was provided within three days, as it was for 17 of 54 children (32%), the relative risk of contracting measles (versus the risk for unvaccinated children) was 0.1 (95% CI, 0.01 to 0.6); however, the observed relative risk did not reach statistical significance among the remaining 37 of 54 (68%) for whom the vaccine was administered within four to five days (RR 0.5; 95% CI, 0.2 to 1.1), six to seven days (RR 0.6; 95% CI, 0.3 to 1.3), or eight to nine days (RR 0.2; 95% CI, 0.03 to 1.3). The

number of children in each of the groups vaccinated beyond the three-day window was not reported. The effectiveness of Ig delivery within — versus outside — the recommended time frame could not be addressed, as the single study reporting on the impact of Ig for PEP[16] did not report use of Ig outside the three- to seven-day window post-exposure as recommended in Australia.

c) **Effect of different concentrations of immunoglobulin:** This subgroup analysis could not be conducted, as the single study reporting on the impact of Ig for PEP[16] did not report details about the dosage or type of Ig used, aside from reference to the product as normal human Ig (NHIG).

d) **Hospitalizations and deaths in high-risk versus lower-risk contacts:** This subgroup analysis could not be conducted, as relevant data for the groups of interest were not reported.

6. DISCUSSION

6.1 Summary of Evidence

Canadian guidelines for the prevention and control of measles outbreaks[9] make a number of recommendations, including isolation of measles cases until four days after rash onset; immunization of susceptible contacts who are willing and able to be immunized within 72 hours of exposure; Ig for susceptible contacts who cannot be immunized within a treatment window of 72 hours to less than six days of exposure; and quarantine of susceptible contacts who are unwilling or unable to receive vaccine or Ig.

This systematic review aimed to determine the effectiveness of interventions commonly used to prevent the secondary spread of measles, with five research questions that explored the evidence regarding measles vaccination of susceptible contacts; administration of Ig to susceptible contacts; quarantine of susceptible contacts; isolation of measles cases; and vaccination clinics or activities above and beyond routine vaccination services to increase population immunization coverage.

Limited evidence met the inclusion criteria established for this review, in which boundaries were set around dates of publication and eligible countries to reflect current vaccination strategies and public health systems similar to those in Canada. Seven comparative observational studies (six retrospective cohort studies and one retrospective case-control study) were identified from Australia (n = 1), Canada (n = 3), Spain (n = 1), Switzerland (n = 1) and the UK (n = 1), with outbreaks spanning the years 1990 to 2007.

With respect to measles vaccination of susceptible contacts, five studies met the inclusion criteria. Two of the studies showed statistically significant benefit to immunization (RR 0.14; 95% CI, 0.02 to 0.98[7] and OR 0.23; 95% CI, 0.11 to 0.50)[15] and three did not.[14,16,17] In two studies, the results were not statistically significant (RR 0.13; 95% CI, 0.01 to 2.15[16] and RR 0.72; 95% CI, 0.18 to 2.8).[14] In the fifth study,[17] there was no benefit to vaccine administration (RR 1.0).

With respect to administration of Ig to susceptible contacts, an Australian study[16] provided comparative results of Ig administration from days 4 to 7 post-exposure for those who missed the three-day post-exposure window required for measles vaccination. Results showed a reduced risk of contracting measles for those administered Ig, although the result was not statistically significant (0.24; 95% CI, 0.06 to 1.06). However, this study described the local guidelines for Ig administration as being within seven days of contact, whereas the Canadian guidelines[9] advise Ig if contact occurred in a window of 72 hours to less than six days.

With respect to quarantine of susceptible contacts, the one identified study from Switzerland[18] showed a statistically significant reduction in the relative risk of contracting measles versus no quarantine (RR 0.26; 95% CI, 0.06 to 0.56). No studies were located that reported on subsequent disease spread for isolation of measles cases.

For the final research question, a study from Inuit communities in northern Canada reported on a special program launched to immunize infants aged six to 11 months in the face of a local outbreak. A statistically significant benefit was observed for the 56 infants immunized versus 23 unimmunized (RR 0.27; 95% CI, 0.11 to 0.68).

Due to the intensity of labour and resource implications required to identify contacts of measles cases, including difficulties obtaining laboratory confirmation of the disease in at least some of the cases, in a real-world setting it seems that a number of susceptible contacts will be identified too late to receive measles vaccine within three days of exposure or Ig within six days of exposure, as recommended in measles control advice. The Spanish authors[7] noted the logistical challenges involved in mounting a rapid effective public health response, including reporting the suspected case within 24 hours of diagnosis, implementing active surveillance, and ensuring close coordination between physicians and public health practitioners. The earliest included Canadian study[15] also noted the significant public health resources needed to conduct an urgent revaccination campaign and thus its feasibility — in their case, reviewing vaccination records in 10 schools, distributing and collecting 8,500 consent letters, and providing 10 school-based clinics (only four were possible after two reported cases).

A 2014 Cochrane review on administration of Ig (i.e., passive immunization) for preventing measles in susceptible contacts was identified that was based on one RCT, two quasi-RCTs, and 10 cohort studies (3,925 participants).[20] The objective of the Cochrane review was to assess the effectiveness and safety of Ig to prevent measles when administered to exposed susceptible people before the onset of symptoms. The authors concluded that Ig given within seven days of exposure was effective at preventing measles, with the risk for non-immune people up to 83% less than if no treatment was given. They also concluded that appropriate use of Ig led to a statistically significant reduction in deaths from measles. This systematic review supports the results of our current review, in which a non-significant trend was observed for the administration of Ig to susceptible contacts. The difference in strength of results is likely attributable to the smaller number of studies included in our review. There was crossover of only one study (Sheppeard 2009).[16] The other studies in the Cochrane review were ineligible for our analysis, based on date of publication (1920 to 1972) and country restrictions used within our review to increase the relevance to the current Canadian context.

Another Cochrane review published in 2012 assessed the effectiveness and safety of MMR vaccine in children up to 15 years of age, as primary prevention of these childhood diseases.[21] Results suggested that one MMR vaccine dose is 92% effective in preventing secondary measles cases among household contacts, but the single included study did not fit with our country-based parameters.

6.2 Limitations

A limited amount of comparative evidence was available from the countries identified as being similar to Canada with respect to vaccination rates and programs, and socioeconomic status. There were a number of studies available from the developing world, but these were excluded due to their lack of similarity to the Canadian context; for example, they had lower immunization rates, different measles outbreak rates, and different public health response strategies. It is possible the amount of available comparative evidence is further limited by publication bias, as it is likely that not all public health responses to measles outbreaks resulted in a scientific publication.

While literature was identified to address four of five research questions, three of the four were limited to a single study. All included studies were of retrospective observational design, and therefore are at higher risk of bias than experimental studies. While RCTs are preferred for evaluating interventional efficacy, none were identified for our review. However, in a measles outbreak situation, RCTs would be difficult for logistical and ethical reasons. The number of

events within the studies was small, with a median of 20 cases of measles among contacts (mean 61; range 1 to 223). Also, half the studies were conducted in the nineties (1994 and 1996), and vaccines, schedules, and population immunization rates have evolved since that time.

The quality of the evidence was limited by issues related to external and internal validity. With respect to external validity, it was not always clear that the populations studied were representative of the larger populations from which they were drawn. Generalizability of results is further complicated because studies were conducted in different countries with different health systems, resources, and staff training, and the span of outbreak years was considerable (1990 to 2007) and vaccination and outbreak control strategies have evolved over that time.

With respect to internal validity, a number of issues were identified, such as lack of controlling for potential confounders, lack of appropriate follow-up, and lack of reliable outcome and exposure assessment. Further, across included studies there was variation in definitions of types of cases and contacts, extent of laboratory confirmation of the disease, and methods of data-gathering. There was also variation across studies in co-interventions, ranging from no additional intervention[7,17] to extensive co-interventions.[16,18] For example, one study involved extensive co-interventions, including[16] advising contacts about the symptoms of measles and how to avoid infecting other people; mass media messages; enhanced surveillance using direct communication via faxes to general practitioners, hospitals, child care centres, and laboratories to raise awareness of the outbreak; and extension of eligibility for free MMR vaccine from general practitioners to all susceptible persons in the state. The co-interventions may have had an impact on the overall effectiveness of the public health intervention, while in such studies the independent impact of the intervention cannot be determined and thus compared with the impact observed among studies with no co-interventions.

7. CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Measles is a highly infectious disease among the unimmunized population, and each case may infect 12 to 18 others.[4,22] Fortunately, measles-containing vaccine is effective for primary prevention of disease, although vaccination of 95% of the population is required to protect those who are susceptible.[4] In Canada, MMR vaccine is currently given to infants at age 12 to 15 months, with a second dose at 18 months up to school entry age.[4] The efficacy of a single injection at 12 to 15 months is estimated to be 85% to 95% and, with a second dose, efficacy in children approaches 100%.[4] Adults born before 1970 are presumed to have acquired natural immunity, although some people may be susceptible.[4]

Due to effective immunization campaigns, endemic measles has been eliminated in many countries, including Canada; however, cases still occur due to importations from other countries and increasing pools of susceptible patients.[23] Measles is currently endemic in much of the world, including Europe, which provides an ongoing source of imported cases.[2] The World Health Organization set a goal of eliminating measles in Europe by the end of 2010, although this was subsequently postponed to 2015.[24]

Endemic measles was declared eliminated in Canada in 1998[4] and in the United States in 2000.[23] Due to decreased uptake in childhood MMR immunization, pools of susceptible patients and resulting outbreaks are causing public health concern.[25] For example, a recent Canadian outbreak occurred in British Columbia's Fraser Valley in the spring of 2014. Low immunization rates at schools where many parents opposed immunization led to nearly 400 cases of measles over four weeks.[26] In contrast, there were 17 reported cases of measles in British Columbia in the previous year.[27] For context, Canadian data show that the median

number of reported measles cases per year across the entire country from 1998 to 2013 was 21.5 cases (range: six to 752).[4]

Elsewhere, the crude incidence rate of laboratory-confirmed measles in England and Wales has risen steeply since 2000 and is now at an 18-year high.[25] In England in 2011-2012, 93% of children had received the first MMR dose but only 86% had had the second dose — significantly below the target 95% threshold to achieve herd immunity.[25] Similarly, in 2011, the United States reported its highest number of measles cases in 15 years.[5] Measles immunization rates have not fallen off dramatically in Canada, although the most recent data are from 2011. For that year, when the Public Health Agency of Canada validated its national immunization coverage survey against local immunization records, it found that 95.2% of two-year-olds had received at least one dose of measles-containing vaccine and 94.9% of seven-year-olds had received at least two doses.[28]

In our report, evidence from a limited number of observational studies showed that several public health interventions to prevent secondary spread of measles may have some benefit, such as immunization of susceptible contacts with measles vaccine and quarantine of susceptible contacts. These two strategies are consistent with the public health advice contained in recent Canadian guidelines on the prevention and control of measles outbreaks.[9] A special within-outbreak program that immunized infants aged six to 11 months also showed a benefit. However, statistically significant results were reported from only two of the five retrieved studies for vaccination of susceptible contacts. The single included study reporting on use of Ig within seven days of contact showed a benefit that did not reach statistical significance (this intervention is recommended in the Canadian guidelines). No literature on the results of isolation of measles cases was eligible for this review.

All included studies were limited by a number of issues related to external and internal validity, such as location in different countries with different health systems, resources, and staff training; lack of laboratory confirmation in many cases; and delays in diagnosis and confirmation that prevented prophylactic treatment. Public health response to measles outbreaks is also limited due to difficulty determining the date of exposure(s) with widespread measles activity; difficulty determining the efficacy of immunizing susceptible contacts when their previous vaccine histories are unclear or unknown; the possibility that Ig retrieved from current blood donations is not as effective as it once was, as many blood donors are immune through immunization rather than through prior measles infection; and practical compliance difficulties in implementing isolation of cases and quarantine of susceptible contacts.

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APPENDIX 1: DEFINITIONS

The Public Health Agency of Canada has definitions related to measles and outbreaks.[9] (Additional references are cited within the table where the report's advisors preferred other wording.)

Term	Definition
Imported case	A confirmed case, which, as supported by epidemiological and/or virological evidence, was exposed to the measles virus outside of Canada during the 7 to 18 days before onset of fever, or 7 to 21 days before onset of generalized rash.
Endemic case	In Canada, endemic measles refers to the situation in which a chain of transmission continues uninterrupted for a period greater than 12 months.
Confirmed case	Confirmed case Laboratory confirmation of infection in the absence of recent immunization with measles-containing vaccine: • isolation of measles virus from an appropriate clinical specimen OR • detection of measles virus RNA OR • seroconversion or a significant (e.g., four-fold or greater) rise in measles IgG titre by any standard serologic assay between acute and convalescent sera OR • positive serologic test for measles IgM antibody using a recommended assay in a person who is either epidemiologically linked to a laboratory-confirmed case or has recently travelled to an area of known measles activity OR • clinical illness in a person with an epidemiologic link to a laboratory-confirmed case.
Probable case	Clinical illness • in the absence of appropriate laboratory tests OR • in the absence of an epidemiologic link to a laboratory-confirmed case OR • in a person who has recently travelled to an area of known measles activity.
Clinical case	Clinical illness is characterized by all of the following features: • fever of 38.3°C or higher • cough, coryza, or conjunctivitis • generalized maculopapular rash for at least 3 days.
Measles outbreak	As measles has been eliminated in Canada, a single case would be considered unusual or unexpected. However, while measles activity remains high in other WHO regions, importations are expected to continue. The following is a working definition of a measles outbreak: two or more confirmed cases linked either epidemiologically or virologically or both.
Susceptible individual	An individual considered susceptible to measles meets one or more of the following criteria: • lack of documented evidence of two doses of measles-containing vaccine • lack of laboratory evidence of prior measles infection; or • lack of laboratory evidence of immunity (i.e., "reactive" or "positive" anti-measles IgG antibody or a previous measles antibody level of ≥ 200 mIU per mL). Note: individuals born before 1970 are presumed to have acquired natural immunity to measles, and are not considered susceptible. The exception is health care workers, who must meet the above criteria, regardless of year of birth.[29]
Contact	A contact is defined as any individual who has: • spent any length of time in a room or enclosed space with a confirmed measles case during that case's infectious period (i.e., approximately 4 days before rash onset to 4 days after rash onset) OR • spent time in a room previously occupied by a measles case, during that case's infectious period, within 2 hours after that individual left the room or space.

Term	Definition
High-risk contact	Any susceptible individual who falls into one or more of the following categories: • pregnant • infant • immunocompromised.
Exposure	Proximity to and/or contact with the measles virus in such a manner that effective transmission of the virus may occur.[30]
Isolation	Isolation is an intervention applied to measles cases whereby the case is separated from non-cases, in order to prevent transmission of the virus.[31] This can include self-isolation or mandated isolation (e.g., through *Immunization of School Pupils Act*.[32])

IgG = immunoglobulin G; IgM = immunoglobulin M; RNA = ribonucleic acid; WHO = World Health Organization.
Source: Unless otherwise indicated, the definitions are those used in the PHAC 2013 Guidelines.[9]

Note regarding "susceptible contact": There are additional situations in which a person may be considered susceptible to severe morbidity or mortality when an outbreak occurs. These high-risk contacts include infants (protection afforded by maternal antibody may be inadequate), immunocompromised individuals, and pregnant women. Examples of primary and secondary immunodeficiency for which the live measles vaccine is contraindicated are provided in the Canadian Immunization Guide.[29]

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	OvidSP
Databases:	Embase <1974 to 2014 September 24> (oemezd) Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to present> (pmez) EBM Reviews - Cochrane Central Register of Controlled Trials <August 2014> (cctr) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 25, 2014
Alerts:	Monthly search updates will begin September 26, 2014, and will continue until project completion.
Study Types:	Not limited by study design
Limits:	Publication years 1994-current; English and French language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
pmez	Ovid database code for MEDLINE database
oemezd	Ovid database code for Embase database
cctr	Ovid database code for Cochrane Central database

MULTI-DATABASE STRATEGY

Line #	Searches
1	Measles/ or Measles virus/ or exp Measles vaccine/
2	(measle* or rubeola or morbillivirus or morbilli).ti,ab.
3	1 or 2
4	Contact tracing/
5	(contact* adj4 (trac* or identif* or detect* or exam* or name* or case* or control or trace or tracing 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.
6	contacts.ti,ab. or contact*.ti. or time to contact.ti,ab. or susceptible.ti. or susceptibles.ti,ab.
7	(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 adolescen* or teen* or youth or youths or population* or communit*)).ti,ab.
8	(suspected adj3 (patient* or case* or contact*)).ti,ab.
9	(measle* adj2 (exposed or exposure)).ti,ab.
10	(unimmuniz* or unimmunis* or underimmuniz* or underimmunis* or under-immuniz* or under-immunis* 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.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
11	("not" adj2 vaccinated).ti,ab.
12	(fail* adj4 vaccinat*).ti,ab.
13	(secondary adj2 (spread or attack* or transmission*)).ti,ab.
14	(case adj (finding or detect* or identif*)).ti,ab.
15	or/4-14
16	Hospitals, Isolation/ or Patient isolation/ or Patient isolators/ or Quarantine/ or isolation.ti.
17	Isolat*.ti,ab. and (Cross Infection/ or exp Disease Transmission, infectious/ or exp Disease outbreaks/ or exp Communicable Diseases/ or Infection Control/)
18	(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.
19	(isolat* and (import* adj4 (case or cases or virus or disease))).ti,ab.
20	((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.
21	(quarantin* or quarantain* or cohorting or cohort nursing or superisolation or isolette* or droplet precaution* or reverse isolation).ti,ab.
22	or/16-21
23	exp Vaccination/ or exp Immunoglobulins/ or exp Measles vaccine/
24	(vaccinat* or immuniz* or immunis* or immunoglobulin* or immune globulin* or vaccine* or inoculat*).ti,ab.
25	23 or 24
26	exp Disease outbreaks/
27	(outbreak* or importation* or secondary spread or secondary transmission*).ti,ab.
28	((epidemic* or pandemic*) adj4 measle*).ti,ab.
29	26 or 27 or 28
30	((target* or outbreak*) adj3 (response* or campaign* or strateg*)).ti,ab.
31	((target* or outbreak*) adj (vaccinat* or immuniz* or immunis* or inoculat*)).ti,ab.
32	30 or 31
33	3 and (15 or 22)
34	3 and 25 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 identif* 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.
43	(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 adolescen* or teen* or youth or youths or population* or communit*)).ti,ab.
44	(suspected adj3 (patient* or case* or contact*)).ti,ab.
45	(measle* adj2 (exposed or exposure)).ti,ab.
46	(unimmuniz* or unimmunis* or underimmuniz* or underimmunis* or under-immuniz* or under-immunis* 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.
47	("not" adj2 vaccinated).ti,ab.
48	(fail* adj4 vaccinat*).ti,ab.
49	(secondary adj2 (spread or attack* or transmission*)).ti,ab.
50	(case adj (finding or detect* or identif*)).ti,ab.

MULTI-DATABASE STRATEGY	
Line #	**Searches**
51	or/40-50
52	Isolation.ti.
53	isolat*.ti,ab. and (Cross Infection/ or Hospital Infection/ or exp Disease Transmission/ or Infection control/ or Import disease/)
54	(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.
55	(isolat* and (import* adj4 (case or cases or virus or disease))).ti,ab.
56	((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.
57	(quarantin* or quarantain* or cohorting or cohort nursing or superisolation or isolette* or droplet precaution* or reverse isolation).ti,ab.
58	or/52-57
59	Vaccination/ or Measles vaccination/ or Revaccination/ or Measles vaccine/ or exp Immunoglobulin/ or Mass immunization/
60	(vaccinat* or immuniz* or immunis* or immunoglobulin* or immune globulin* or vaccine* or inoculat*).ti,ab.
61	59 or 60
62	Import disease/ or Epidemic/ or Pandemic/
63	(outbreak* or importation* or secondary spread or secondary transmission*).ti,ab.
64	((epidemic* or pandemic*) adj4 measle*).ti,ab.
65	62 or 63 or 64
66	((target* or outbreak*) adj3 (response* or campaign* or strateg*)).ti,ab.
67	((target* or outbreak*) adj (vaccinat* or immuniz* or immunis* or inoculat*)).ti,ab.
68	66 or 67
69	(3 and (15 or 22)) or (3 and 25 and 29) or (3 and 32)
70	(39 and (51 or 58)) or (39 and 61 and 65) or (39 and 68)
71	69 use pmez
72	69 use cctr
73	70 use oemezd
74	73 not conference abstract.pt.
75	71 or 72 or 74
76	limit 75 to yr="1994 -Current"
77	limit 76 to (english or french)
78	remove duplicates from 77

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

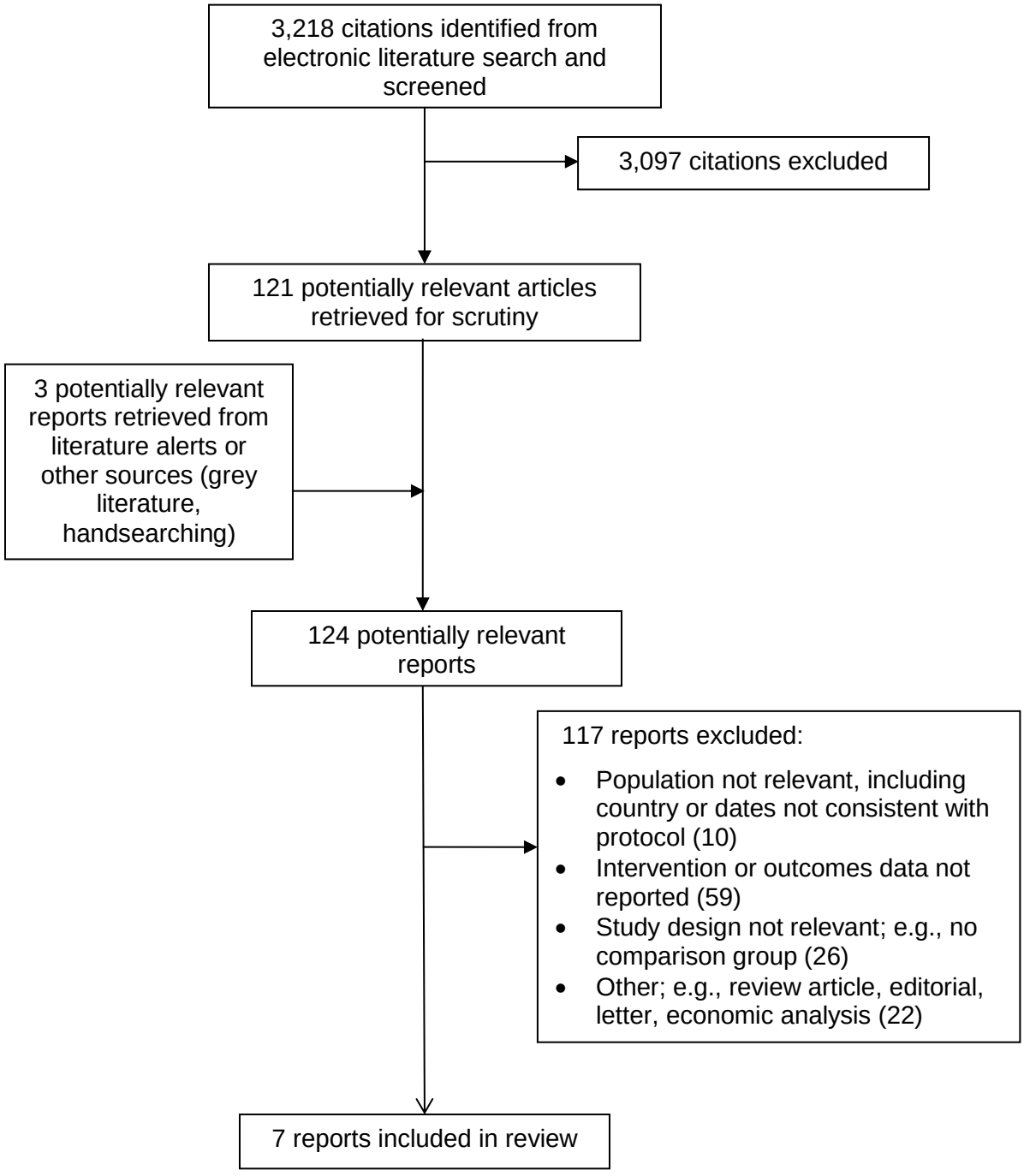
Grey Literature

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.

APPENDIX 3: SELECTION OF INCLUDED STUDIES



APPENDIX 4: INCLUDED STUDIES FOR CLINICAL EVIDENCE

Barrabeig I, Rovira A, Rius C, Munoz P, Soldevila N, Batalla J, et al. Effectiveness of measles vaccination for control of exposed children. Pediatr Infect Dis J. 2011 Jan;30(1):78-80.

Delaporte E, Wyler Lazarevic CA, Iten A, Sudre P. Large measles outbreak in Geneva, Switzerland, January to August 2011: descriptive epidemiology and demonstration of quarantine effectiveness. Euro Surveill. 2013;18(6):1-8.

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APPENDIX 5: EXCLUDED STUDIES FOR CLINICAL EVIDENCE (AND REASONS)

A. Population not of interest

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Edelson PJ. Quarantine and Social Inequity. JAMA. 2003;290(21):2874.

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B. Intervention not of interest (i.e., no discussion of contacts management) and/or outcomes or data not reported for contacts

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Centers for Disease Control and Prevention (CDC). Outbreak of measles--Venezuela and Colombia, 2001-2002. MMWR Morb Mortal Wkly Rep. 2002 Aug 30;51(34):757-60.

Centers for Disease Control and Prevention (CDC). Measles outbreak among internationally adopted children arriving in the United States, February-March 2001. MMWR Morb Mortal Wkly Rep. 2002 Dec 13;51(49):1115-6.

Centers for Disease Control and Prevention (CDC). Imported measles case associated with nonmedical vaccine exemption--Iowa, March 2004. MMWR Morb Mortal Wkly Rep. 2004 Mar 26;53(11):244-6.

Centers for Disease Control and Prevention (CDC). Import-associated measles outbreak--Indiana, May-June 2005. MMWR Morb Mortal Wkly Rep. 2005 Oct 28;54(42):1073-5.

Centers for Disease Control and Prevention (CDC). Measles--United States, January 1-April 25, 2008. MMWR Morb Mortal Wkly Rep. 2008 May 9;57(18):494-8.

Centers for Disease Control and Prevention (CDC). Progress toward measles elimination--European Region, 2005-2008. MMWR Morb Mortal Wkly Rep. 2009 Feb 20;58(6):142-5.

Centers for Disease Control and Prevention (CDC). Increased transmission and outbreaks of measles--European Region, 2011. MMWR Morb Mortal Wkly Rep. 2011 Dec 2;60(47):1605-10.

Centers for Disease Control and Prevention (CDC). Hospital-associated measles outbreak - Pennsylvania, March-April 2009. MMWR Morb Mortal Wkly Rep. 2012 Jan 20;61(2):30-2.

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APPENDIX 6: CLINICAL EVIDENCE — STUDY CHARACTERISTICS

Table 6-1: Study Characteristics for Research Question 1 — Vaccination of Susceptible Contacts					
Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
Country	Spain	Australia (NSW)	UK	Canada	Canada
Dates of outbreak	August 2006 to June 2007	March 1 to May 31, 2006	NR	April 13 to June 12 1995	September 1 to December 31, 1990
Study objective	To assess MMR vaccine effectiveness as PEP in children in child care and school	To assess the effectiveness of MMR vaccine within 3 days of exposure (or Ig within 7 days of exposure) as PEP during an outbreak	To assess the effectiveness of MMR vaccination as PEP among susceptible close contacts	To assess measles vaccine effectiveness as PEP during a high school outbreak	To assess the effectiveness of measles revaccination of students as PEP during a school measles outbreak
Study design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective matched case-control; 1:2 match of measles cases to controls randomly selected from same homeroom class as cases
Population	Children at child care centres and schools of Barcelona area	NSW residents	Children at a nursery	Students at a Toronto high school	Previously immunized children attending 31 schools in Mississauga with measles outbreaks
Definitions					
Confirmed case	Laboratory-confirmed case (positive IgM antibody by ELISA or positive urine PCR) or clinical case as per WHO definition + linked to a laboratory-confirmed case	Laboratory-confirmed case (positive IgM) w/ compatible clinical illness; or virus detection via IF or PCR or culture; or clinical S&S (one or more of fever, cough, coryza, conjunctivitis, and MP rash) w/ link to a laboratory-confirmed case	NR	NACI or modified definition (positive IgM antibody or virus detection or four-fold rise in antibody titre or clinical case linked to a laboratory-confirmed case)	ACE: temp ≥ 38.3°C + cough, coryza, or conjunctivitis, followed by generalized MP rash for 3+ days. Also required: positive IgM antibody or virus detection or four-fold rise in antibody titre or clinical case linked to a laboratory-confirmed case
Index case	First case of measles in the classroom	NR	First case of measles in the nursery	High school student — PH notified of positive laboratory results	Student who had received measles-rubella vaccine at 5 months of age

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Secondary case	A contact with rash onset 7 to 18 days after rash onset in the index case	NR	NR	NR	NR
Contact	Child who had shared the same classroom as the index case for at least 1 day during the infectious period (4 days before and 4 days after onset of rash)	Anyone who was in the same room as the case, or the same room for up to 2 hours after the case, during the infectious period	Child who had been in close contact (not defined)	NR	Students from same classroom as confirmed measles cases
Susceptible contact	No previous measles vaccine or measles	Inadequate immunity to measles; i.e., age 6 to 12 months, age 1 to 4 years without MMR, age 4 years to adults born after 1996 without 2 MMR doses	Unimmunized	Born after 1956 with no previous measles vaccine or laboratory-confirmed measles, or previous measles vaccine before first birthday with no previous measles (A few people [7 of 954] who were "inadequately vaccinated" [i.e., had one dose before the outbreak but after their first birthday] also chose to receive the intervention during the outbreak.)	NR
Time to intervention	Period between rash onset of the index case and the day of vaccination of the susceptible contact (median: 5 days; range 1 to12 days)	MMR within 3 days of exposure, or Ig within 7 days of exposure	Period between laboratory diagnosis of the index case and the day of vaccination of the susceptible contact. Time to intervention NR for study subjects	NR	NR
How data were collected	Written immunization records from PH units	Surveillance officers collected data on S&S of measles cases through interview of cases (or	NR	Active case finding by PH staff and notification by laboratories and physicians. Vaccination	Measles cases reported to PH and verified against the case definition; exposed controls randomly selected from same

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		their parents) and their health care providers, and recorded on a standard reporting form. Case interviews were also used to identify possible contacts		details were obtained through Ontario's computerized Immunization Record Information System, maintained by PH	classroom as cases; vaccination details in school records confirmed with parents or physicians by the investigator
Intervention	MMR vaccine to susceptible contacts (1 to 12 days after exposure)	MMR within 3 days of exposure (or Ig within 7 days of exposure)	MMR vaccine to susceptible contacts the day of laboratory diagnosis of index case	First dose of measles vaccine to susceptible contacts during outbreak	Revaccination with measles vaccine during outbreak, if 2 or more cases at a school
Co-interventions	None	Interviews with affected person or carer, including advice about minimizing spread; contact tracing; mass media messages; direct communication to physicians, hospitals, child care centres, and laboratories to raise awareness; extension of eligibility for free MMR vaccine from general practitioners to susceptible persons	NR	Exclusion of unvaccinated children from school until 2 weeks after onset of last case; exclusion of students with measles for 5 days after rash onset	Contract tracing, vaccination of susceptible contacts, revaccination of contacts vaccinated before January 1, 1980, exclusion of unvaccinated children from school until 2 weeks after onset of last case
Outcome (effect measure)	Incidence of measles (RR)	Incidence of measles (RR)	Incidence of measles (RR)	Incidence of measles (RR)	Incidence of measles (OR)

ACE = Advisory Committee on Epidemiology; ELISA = enzyme-linked immunosorbent assay; IF = immunofluorescence; Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; MP = maculopapular; NACI = National Advisory Committee on Immunization; NR = not reported; NSW = New South Wales; OR = odds ratio; PCR = polymerase chain reaction; PE = prophylaxis effectiveness; PEP = post-exposure prophylaxis; PH = public health; RR = relative risk; S&S = signs & symptoms; w/ = with; WHO = World Health Organization.

Table 6-2: Study Characteristics for Research Question 2 — Immunoglobulin for Susceptible Contacts	
Author, Year	**Sheppard et al., 2009[16]**
Country	Australia
Outbreak dates	March 1 to May 31, 2006
Objective of study	To assess the effectiveness of MMR vaccine within 3 days of exposure or Ig within 7 days of exposure as PEP during an outbreak
Study design	Retrospective cohort study
Population	NSW residents
DEFINITIONS	
Confirmed case	Laboratory-confirmed case (positive IgM) w/ compatible clinical illness; or virus detection via IF or PCR or culture; or clinical S&S (one or more of fever, cough, coryza, conjunctivitis, and MP rash) w/ link to a laboratory-confirmed case
Index case	NR
Secondary case	NR
Contact	Anyone who was in the same room as the case, or the same room for up to 2 hours after the case, during the infectious period
Susceptible contact	Inadequate immunity to measles, i.e., age 6 to 12 months; age 1 to 4 years without MMR; age 4 years to adults born after 1996 without 2 MMR doses
Time to intervention	MMR within 3 days of exposure, or Ig within 7 days of exposure
How data were collected	Surveillance officers collected data on S&S of measles cases through interview of cases (or their parents) and their health care providers, and recorded on a standard reporting form. Case interviews were also used to identify possible contacts
Intervention	MMR within 3 days of exposure or Ig within 7 days of exposure
Co-intervention	Interviews with affected person or carer, including advice about minimizing spread; contact tracing; mass media messages; direct communication to physicians, hospitals, child care centres, and laboratories to raise awareness; extension of eligibility for free MMR vaccine from general practitioners to susceptible persons from May 18, 2006
Outcome (effect measure)	Incidence of measles (RR)

IF = immunofluorescence; Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; MP = maculopapular; NR = not reported; NSW = New South Wales; PCR = polymerase chain reaction; PEP = post-exposure prophylaxis; RR = relative risk; S&S = signs & symptoms; w/ = with.

Table 6-3: Study Characteristics for Research Question 3 — Quarantine of Susceptible Contacts	
Author, Year	**Delaporte et al., 2013**[18]
Country	Switzerland
Outbreak dates	January 1 to August 31, 2011
Objective of study	To assess the effectiveness of quarantine on measles transmission during an outbreak
Study design	Retrospective cohort study
Population	Residents of the Canton of Geneva, Switzerland
DEFINITIONS	
Confirmed case	*Laboratory-confirmed case*: Positive laboratory test (IgM or PCR) plus at least one of: MP rash, fever, cough, coryza, or conjunctivitis *Epidemiologically linked case*: MP rash and fever and any of cough, coryza, or conjunctivitis + link to a laboratory-confirmed case
Probable case	MP rash and fever and any of cough, coryza, or conjunctivitis with no link to a laboratory-confirmed case
Possible case	Did not meet all clinical criteria, plus no laboratory-positive result
Index case	Not known to be related to other measles cases
Secondary case	NR
Contact	Exposed to the case during the contagious period (4 days before to 4 days after rash onset)
Susceptible contact	Born after 1963 and without vaccination or IgG or proven history of measles
Time to intervention	After last contact or after rash onset of the case. Time to intervention NR for study subjects
How data were collected	Cases reported through the notification system or by active case finding
Intervention	Quarantine for 18 days after last contact (for contacts)
Co-interventions	Contact tracing; letters to parents of school and nursery school children; press releases; emails to university students; letters to high school students, school directors, and day care centres; emails to local physicians with updates and advice for outbreak control
Outcome (effect measure)	Incidence of measles (RR)

IgG = immunoglobulin G; IgM = immunoglobulin M; LHA = local health authority; MP = maculopapular; NR = not reported; PCR = polymerase chain reaction; RR = relative risk.

Table 6-4: Study Characteristics for Research Question 5 — Targeted Measles Vaccination Activities During an Outbreak	
Author, Year	**De Serres et al., 1996[19]**
Country	Canada
Outbreak dates	August to September, 1991
Study objective	To assess vaccine effectiveness in children aged 6 months to 11 months given monovalent measles vaccine for outbreak control (Note: 11 months means in the child's 11th month; i.e., < 12 months)
Study design	Retrospective cohort study
Population	Children aged 6 to 11 months in 8 Inuit communities in northeastern Quebec
Definitions	
Confirmed case	Fever > 38.3°C, generalized rash, and at least one of cough, coryza, or conjunctivitis
Index case	26-year-old male developed measles August 11
Secondary case	NR
Contact	NR
Susceptible contact	Aged 6 to 11 months (all were unvaccinated)
Intervention time	Started 19 days after index case became ill (August 30)
How data were collected	Active surveillance by nurses in the communities, including weekly reporting
Intervention	Monovalent measles vaccine for age 6 to 11 months
Co-interventions	None for this population, although simultaneously MMR II vaccine was administered to those born after 1957 but vaccinated before 1980; unvaccinated persons ≥ 1 year were vaccinated, and infants < 6 months of age were administered Ig
Outcome (effect measure)	Incidence of measles

Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; NR = not reported.

APPENDIX 7: CLINICAL EVIDENCE — CRITICAL APPRAISAL OF STUDIES

Table 7-1: Critical Appraisal of Studies for Research Question 1 — Vaccination of Susceptible Contacts					
Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
External validity					
Patients representative of the entire population from which they were recruited	Likely — this was a population-based sample, although there was no comparison to population characteristics. It was unclear whether the unvaccinated measles cases and their contacts were similar to the general population.	Unknown — this was a population-based sample, although there was no comparison to population characteristics and no description of the distribution of measles cases within the population. Some contacts were managed by GPs versus PH, and were excluded from the study. Unclear whether there were differences in characteristics among populations.	Unknown — unclear whether the children enrolled in this one small nursery school were representative of other similar populations.	Yes for age and sex	Unknown — 31 of 155 schools in the region were included and there was no comparison to local population characteristics.
Internal validity					
Patients recruited from the same population	Yes (school and child care classrooms)	Patients recruited from NSW residents (although contacts treated by GPs or hospitals not included)	Yes (nursery)	Yes	Yes — same classrooms (equal measles exposure)
Groups comparable with regard to important determinants; differences adjusted for in analysis	Patient characteristics NR; confounders not identified; analysis is unadjusted	Patient characteristics NR; analysis is unadjusted	Patient characteristics NR; confounders not identified; analysis is unadjusted	Reported differences in original immunization status: measles group 98.8% coverage vs. 93.8% for non-measles group	Measles cases more likely to have been vaccinated < 1980 (55.2% vs. 40.7%, $P = 0.05$) and < age 12 months (21.2% v. 2.9%, $P < 0.01$)
Valid and reliable measurement of exposure and	Unclear — unclear how initial measles cases were identified,	Unclear (see Table 7-2 for detail)	Measurement of exposure is unclear; measurement of	Yes — suspected and confirmed cases were actively reported, with	Yes — case definitions provided (Advisory Committee

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Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
outcomes for cases and contacts	although all cases were laboratory-confirmed or met WHO definition. Secondary cases identified through active surveillance. Contacts included only classroom contacts. Vaccination (exposure) status obtained through PH database with uncertain completeness or accuracy. Median intervention time was 5 days (range 1 to 12 days), suggesting variable effectiveness.		outcomes was consistent with respect to laboratory confirmation of the diagnosis (measles-specific IgM).	additional active case finding by PH staff. If measles was suspected, phone follow-up assessed whether the illness met the NACI case definition and sought contacts and risk activities (modified case definition used for 3 students without recorded temp.). Vaccination status obtained through PH database with purported but unverified completeness and accuracy. Time from exposure to intervention NR.	on Epidemiology definition); controls selected from same classroom as cases. Time from exposure to intervention NR.
Analysis adjusts for different lengths of follow-up (cohort studies) or time period between the intervention and outcome is the same for cases and controls (case-control studies)	Yes	NR	NR	Yes	Yes
Follow-up sufficiently long and complete	Unclear how long the susceptible contacts were checked for measles once index cases were identified	Follow-up ended May 31, yet 2 cases were reported the week of May 24, meaning further cases were still possible	NR	Perhaps not — follow-up ended after about 9 weeks from outbreak's onset	Yes
Other	Some susceptible contacts were > 15 months old and may have been vaccinated prior to study; unclear if these children were	Delays in clinical and laboratory confirmation of measles and case notification plus delays in identification of potential contacts meant	Detail on this outbreak is limited — reported in 3 paragraphs of a letter to a journal	Outbreak occurred before 2 doses of measles vaccine became routine in Canada	Outbreak occurred before 2 doses of measles vaccine became routine in Canada

Table 7-1: Critical Appraisal of Studies for Research Question 1 — Vaccination of Susceptible Contacts					
Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
	excluded from the study	prophylactic immunization within the recommended time frame was often not possible			Adequate sample size for primary effect measure

GP = general physician; IgM = immunoglobulin M; MMR = measles-mumps-rubella vaccine; NACI = National Advisory Committee on Immunization; NR = not reported; NSW = New South Wales; PEP = post-exposure prophylaxis; PH = public health; RR = relative risk; WHO = World Health Organization.

Table 7-2: Critical Appraisal of Study for Research Question 2 — Immunoglobulin for Susceptible Contacts	
Author, Year	**Sheppard et al., 2009[16]**
External validity	
Patients representative of the entire population from which they were recruited	Unknown — this was a population-based sample, although there was no comparison to population characteristics and no description of the distribution of measles cases within the population. Some contacts were managed by GPs versus PH and were excluded from the study. Unclear whether there were differences in characteristics among populations.
Internal validity	
Patients recruited from the same population	Patients recruited from NSW residents (although contacts treated by GPs or hospitals not included)
Groups comparable with regard to important determinants; differences adjusted for in analysis	Patient characteristics NR; analysis is unadjusted
Valid and reliable measurement of exposure and outcomes for cases and contacts	Unclear • All cases were notified to PH and verified as meeting the case definition. Some secondary cases may not have been identified (did not seek health care or were misdiagnosed). • Potential contacts were identified through case interviews, but success of follow-up with those contacts was NR. Contacts treated by GPs or hospitals were not included; therefore, documentation of some cases was incomplete. • Susceptible contacts were estimated based on Australian guidelines, and not laboratory-confirmed. The authors noted that classification on the basis of age could lead to an over- or underestimation of the number of susceptible contacts (they thought it was likely an overestimate). • All participants received the intervention within a comparable time frame.
Follow-up sufficiently long and complete	Follow-up ended May 31, yet 2 cases were reported the week of May 24, meaning further cases were still possible
Other	Early in the outbreak, delays in clinical and laboratory confirmation of measles and case notification, as well as delays in identification of potential contacts, meant that prophylactic immunization for contacts within the recommended 7 days of exposure was often not possible.

GP = general practitioner; NA = not available; NR = not reported; NSW = New South Wales; PH = public health.

Table 7-3: Critical Appraisal of Study for Research Question 3 — Quarantine of Susceptible Contacts	
Author, Year	**Delaporte et al., 2013[18]**
External validity	
Patients representative of the entire population from which they were recruited	Yes
Internal validity	
Patients recruited from the same population	Patients recruited from Geneva Canton, although 62 additional measles cases diagnosed in Geneva were excluded because they lived in a different country or canton; some worked or attended school in Geneva.
Groups comparable with regard to important determinants; differences adjusted for in analysis	Patient characteristics NR; analysis is unadjusted
Valid and reliable measurement of exposure and outcomes for cases and contacts	Likely • Cases reported were identified via the mandatory notification system or by active case finding. Cases were further reported as confirmed, probable, or possible. Confirmed cases were reported as laboratory-confirmed or epidemiologically linked • Unclear how vaccination status was confirmed to identify susceptible contacts • Unclear how or whether compliance with quarantine was assessed
Analysis adjusts for different lengths of follow-up	NA
Follow-up sufficiently long and complete	Unsure — not clear when the last case was
Other	• 17 close contacts received post-exposure vaccination, of whom 6 developed measles (5 were vaccinated > 72 hours post-exposure) • Siblings and classmates of cases were included as susceptible contacts, although each group would have different exposure due to siblings co-habiting with cases and classmates living separately.

NA = not available; NR = not reported.

Table 7-4: Critical Appraisal of Study for Research Question 5 — Targeted Measles Vaccination Activities During an Outbreak	
Author, Year	**De Serres et al., 1996[19]**
External validity	
Patients representative of the entire population from which they were recruited	Yes
Internal validity	
Patients recruited from the same population	Yes
Groups comparable with regard to important determinants; differences adjusted for in analysis	Risk of exposure was assumed to be the same between groups. Patient age distribution was similar between groups; mean age of mothers and maternal vaccination status was similar between groups, which means their infants should have comparable rates of passive immunity (although no data were provided); other characteristics NR.
Valid and reliable measurement of exposure and outcomes for cases and contacts	Yes. Detection of measles cases was carried out actively in every community; weekly reports were provided by each village for the duration of the outbreak; however, cases were clinically but not laboratory-confirmed. Susceptible contacts were identified through census data. Vaccination exposure was prospectively assessed during the outbreak.
Analysis adjusts for different lengths of follow-up	NA
Follow-up sufficiently long and complete	Yes. Last contact was immunized Sept 12 and follow-up extended to Sept 30. All other contacts were immunized the week starting August 30.
Other	• Data and results for children ≥ 1 year NR (as per study objective) • The 23 infants in the control group were not in the community during the vaccination drive. The number of infants in the community during the outbreak was not reported, however, indicating potential differential exposure to measles virus between study groups.

NA = not available; NR = not reported.

APPENDIX 8: CLINICAL EVIDENCE — STUDY RESULTS

Table 8-1: Results of Studies for Research Question 1 — Vaccination of Susceptible Contacts					
Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
Index cases, n	10	NR	1	1	1
Total cases, n	35	57 total measles cases (index and secondary)	7	87	87 included in case-control study (of 126 who met the case definition)
Exposed contacts, n	166	1,760 (estimated — not laboratory-confirmed)	6	1,048	135 controls
Susceptible contacts (candidates for intervention), N	75	553	6	66	There were 222 participants: 87 measles cases and 135 controls (no participants were susceptible contacts [i.e., unvaccinated]).
Infectious period, days (range)	Median 2 (1 to 4)	NR	3	NR	NR
Age of index case(s)	8 were aged 6 to 14 months; 2 were aged 15 months to 4 years	NR	17 months	NR	17 years
Median age of susceptible contacts (range)	16.5 months (6 to 47 months)	NR	Range 15 to 24 months	NR. Age range for entire school = 14 to 21 years	11.6 years (11 months to 37 years)
Susceptible contacts who received vaccine, n/N (%)	Total: 54/75 (72) Within 3 days of exposure: 17/75 (22.7)	82/553 (15)	4/6 (67%)	26/66 (39.4)	45/135 (33.6) control subjects and 9/87 (10.3) case subjects revaccinated during the outbreak
Susceptible contacts who did not receive vaccine, n/N (%)	21/75 (28)	183 = Ig 288 = no intervention	2/6 (33%)	40/66 (60.6)	90/135 (66.4) control subjects and 78/87(89.7) case subjects were not revaccinated during the outbreak
Median intervention time, days (range)	5 (1 to 12)	NR	3	NR	NR
Incidence of measles, n/N (%)					
Total measles cases	25/75 (33.3)	15/553 (2.7)	7/7 (100)	1/66 (15.2)	87
Measles in contacts who received vaccine	12/54 (22.2)	0/82 (0)	4/4 (100)	2/33 (6.4)	9 measles cases were revaccinated during the outbreak[c]

Table 8-1: Results of Studies for Research Question 1 — Vaccination of Susceptible Contacts					
Author, Year	**Barrabeig et al., 2011[7]**	**Sheppeard et al., 2009[16]**	**Rice et al., 2004[17]**	**Sutcliffe and Rea, 1996[14]**	**Yuan, 1994[15]**
Measles in contacts who received vaccine within 3 days of exposure	1/17 (5.9)	NR	NA	NA	NA
Measles in contacts who did not receive vaccine	13/21 (61.9)	No PEP = 13/288 (4.5) Ig = 2/183 (1.1)	2/2 (100)	83/986 (8.4)	78 cases were not revaccinated during the outbreak[c]
RR or OR (95% CI) for contacts who received vaccine	RR: 0.4 (0.2 to 0.6)	RR: 0.13 (0.01 to 2.15)	RR: 1.0[a]	RR: 0.72 (0.18 to 2.8)[a]	OR: 0.23 (0.11 to 0.50)[b]
RR (95% CI) for contacts who received vaccine within 3 days of exposure	0.14 (0.02 to 0.98)[a]	NA	NA	NA	NA

CI = confidence interval; GP = general practitioner; Ig = immunoglobulin; NA = not applicable; NR = not reported; PEP = post-exposure prophylaxis; RR = relative risk.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php).
[b] Calculated by CADTH (OR calculator) (http://www.medcalc.org/calc/odds_ratio.php).
[c] In this case-control study, by definition, controls did not contract measles.

Table 8-2: Results of Study for Research Question 2 — Immunoglobulin for Susceptible Contacts			
Author, Year	**Sheppeard et al., 2009[16]**		
Index cases, n	NR		
Total cases, n	57 total measles cases (index and secondary)		
Exposed contacts, n	1,760 (estimated — not laboratory-confirmed)		
Susceptible contacts (candidates for intervention), N	553		
Median infectious period, days (range)	NR		
Median age of index cases (range)	NR		
Median age of susceptible contacts, months (range)	NR		
Susceptible contacts who received Ig, n/N (%)	183/553 (33)		
Susceptible contacts who received MMR, n/N (%)	82/553 (15)		
Susceptible contacts with no intervention, n/N (%)	288/553 (52)		
Median intervention time, days (range)	NR		
Incidence of measles. n/N (%)	**MMR within 3 days, or Ig from 4 to 7 days**	**Ig from 4 to 7 days only**	**MMR within 3 days only**
In contacts who received PEP	2/265 (0.8)	2/183 (1.1)	0/82 (0)
In contacts who did not receive PEP	13/288 (4.5)		
Total measles cases	15/553 (2.7)		
PEP effectiveness, % (95% CI)			
MMR within 3 days, or Ig from 4 to 7 days	83.3 (27 to 96)		
Ig from 4 to 7 days	75.8 (0 to 94)		
MMR within 3 days	100 (NR)		
RR[a] MMR or Ig (95% CI)	0.17 (0.04 to 0.73)		
RR[a] Ig within 4 to 7 days (95% CI)	0.24 (0.06 to 1.06)		
RR[a] MMR within 3 days (95% CI)	0.13 (0.01 to 2.15)		

CI = confidence interval; Ig = immunoglobulin; MMR = measles-mumps-rubella vaccine; NA = not applicable; NR = not reported; PEP = post-exposure prophylaxis; RR = relative risk.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php).

Table 8-3: Results of Study for Research Question 3 — Quarantine of Susceptible Contacts	
Author, Year	**Delaporte et al., 2013[18]**
Index cases, n	NR
Total cases	223 total measles cases (195 confirmed cases in Geneva + 16 probable cases in Geneva + 12 cases who were not residents of Geneva)
Exposed contacts, n	NR
Susceptible contacts (candidates for intervention), N	NR
Median infectious period, days (range)	NR
Median age of index, months (range)	NR
Median age of susceptible contacts, months (range)	NR
Susceptible contacts who were quarantined, n/N (%)	73
Susceptible contacts who were not quarantined, n/N (%)	NR
Median intervention time, days (range)	NR
Incidence of measles	
• In contacts who were quarantined, n/N (%)	50/73 (69)
• In contacts who were not quarantined, n/N (%)	173/NR
• Cases arising from measles cases who were quarantined, n/N (%)	6/50 (12)
• Cases arising from measles cases who were not quarantined, n/N (%)	81/173 (47)
SAR reduction	74%
RR (95% CI)	0.26 (0.06 to 0.56)
RR (95% CI) for household members	0.43 (0.09 to 1.00)
RR (95% CI) for community members	0.05 (0.00 to 0.69)

CI = confidence interval; NR = not reported; RR = relative risk; SAR = secondary attack rate.

Table 8-4: Results of Study for Research Question 5 — Targeted Measles Vaccination Activities During an Outbreak	
Author, Year	**De Serres et al., 1996[19]**
Index case, n	1
Total cases, n	15
Exposed contacts (age 6 to 11 months), n	NR
Susceptible contacts (age 6 to 11 months) (candidates for intervention), N	81
Infectious period, days	All those with measles developed it within 10 days of vaccination; i.e., before the vaccine was fully protective
Age of index case	26 years
Median age of susceptible contacts, months (range)	8.5 (6 to 11)
Susceptible contacts (age 6 to 11 months) who received vaccine, n/N (%)	56/81 (69.1)
Ages 6 to 8 months	27/39 (69)
Ages 9 to 11 months	29/42 (69)
Susceptible contacts (age 6 to 11 months) who did not receive vaccine, n/N (%)	23/81(28.4)
Susceptible contacts (age 6 to 11 months) who received Ig, n/N (%) (not included in authors' analysis)	2/81 (2.5)
Median intervention time, days (range)	Vaccination of 55 infants was completed within a week of August 30; remaining 1 vaccinated on September 12
Incidence of measles, n/N (%) (excludes the 2 infants who received Ig)	
• Total measles cases	15/79 (19)
• Measles in contacts who received vaccine	6/ 56 (11)
Ages 6 to 8 months	4 / 27 (15)
Ages 9 to 11 months	2 / 29 (7)
• Measles in contacts who did not receive vaccine	9/ 23 (39)
Ages 6 to 8 months	5 / 11 (45)
Ages 9 to 11 months	4 / 12 (33)
RR (95% CI)[a]	0.27 (0.11 to 0.68)
RR (95% CI) ages 6 to 8 months [a]	0.33 (0.11 to 0.99)
RR (95% CI) ages 9 to 11 months [a]	0.21 (0.04 to 0.98)
RR reduction, measured as VE[b] % (95% CI)	73 (32 to 89)

CI = confidence interval; Ig = immunoglobulin; NR = not reported; RR = relative risk; VE = vaccine effectiveness.
[a] Calculated by CADTH (RR calculator) (http://www.medcalc.org/calc/relative_risk.php).
[b] VE = [(attack rate unvaccinated – attack rate vaccinated) / attack rate unvaccinated] x 100; CI calculated using a Taylor series.