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

Measles outbreaks in Canada

a brief modelling study

16th century drawing (public domain)

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Learning objectives

By the end of this event, participants will be able to:

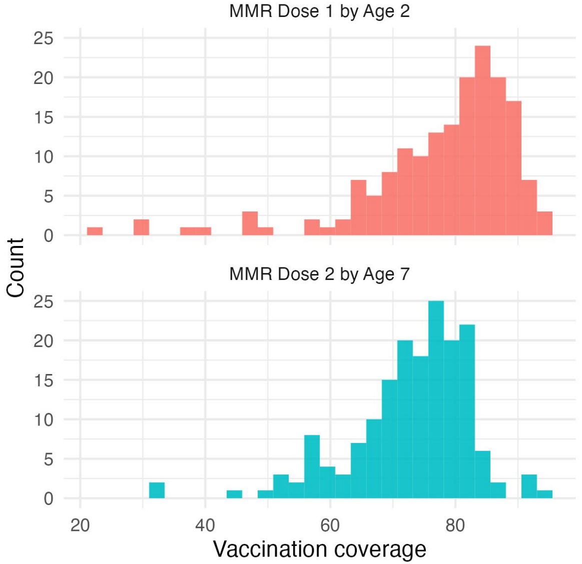
1. Describe the components of a mathematical model for measles
2. Analyze the impacts of different public health interventions and their intensity on measles cases and outbreaks
3. Apply mathematical outputs to public health policy and practice

Background

- Measles has been considered eliminated in Canada since 1998
- Measles is rising globally, and more introductions to Canada will occur
- There have been occasional outbreaks, including large ones, following introductions of measles from endemic areas
  - Quebec > 700 cases in 2011
  - BC > 400 cases in 2014
  - Other sporadic and smaller outbreaks
- Outbreaks are challenging to control, with considerable effort and cost
- Canada has a high (around 90%) measles vaccination coverage overall
- But there are areas and communities with much lower vaccination

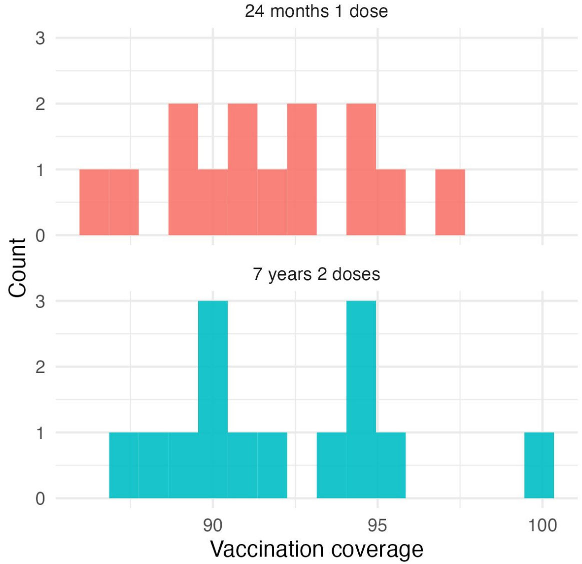
Vaccination variability in Canada: examples

Alberta



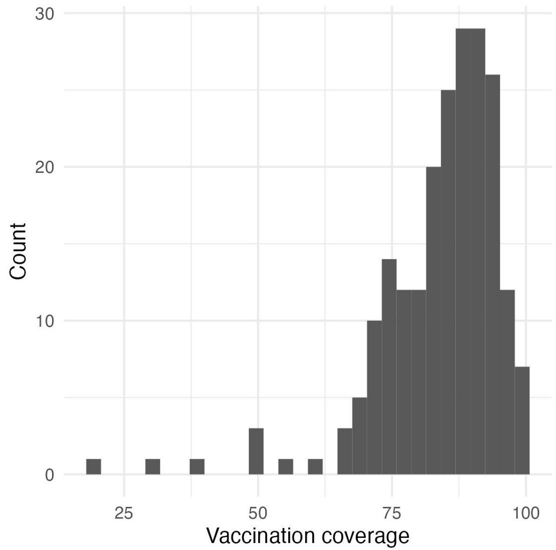
http://www.ahw.gov.ab.ca/IHDA_Retrieval/selectSubCategory.do

Saskatchewan



https://www.saskatchewan.ca/residents/health/accessing-health-care-services/immunization-services/immunization-rates-in-saskatchewan

Vancouver school board



https://public.tableau.com/app/profile/phsu.dashboard/viz/VCHSchoolImmunizationCoverageDashboard/Dashboard

Aims

Given the variability in vaccination coverage in Canadian jurisdictions, and historical outbreak sizes in similar populations:

How large might outbreaks be in Canadian settings?

How does the potential outbreak size vary with vaccination coverage?

How strong do interventions have to be to control outbreaks in lower-vaccination settings?

The model

We use a stochastic model with compartments:

- Susceptible: not immune, not infected, but in the community that is likely to be exposed as the outbreak progresses
- Infected, pre-rash onset. Infectiousness begins 4 days before rash onset). Duration of infection before rash: 10 days
- Infected, post-rash onset. Infectious for 4 days after rash
- Immune: recovered or vaccinated (or previously had measles)

Community sizes:
Small: 1000, modelling a school and close contacts
Larger: 8000, modelling a tight-knit but broader community

Interventions

If vaccination rates are above 95%, measles spread is not sustained (too many people are immune). If vaccination rates are lower, interventions are needed.

These often include:

- post-exposure prophylaxis (PEP): MMR vaccine or immunoglobulin shortly after exposure.
- case finding and isolation for non-immunized people who have been exposed (or exclusion from school or high-risk setting)
- measures to ensure that infectious individuals are asked to isolate and can do so effectively

Parameters and interventions

Course of infection

- Basic reproduction number: 15 (range is typically given as 12-18). This is in the absence of vaccination. With vaccination R is not this high, and is approximately R0 (1 - coverage)
- Duration of the exposed class: 10 days. WHO: rash onset 7-18 days from infection
- Infectious prior to rash: “exposed” individuals are infectious 0.3 times as much as “I” compartment
- Duration of infectious compartment I: 4 days (WHO: infectious 4 days after onset of rash)

Interventions

- post-exposure prophylaxis (PEP): MMR vaccine or immunoglobulin shortly after exposure. **Model:** exposed individuals move to the recovered (immune) class at a rate q_{pep}
- case finding and isolation for exposed non-immunized people. **Model**: susceptible and exposed individuals are asked to isolate and removed to an isolated class at rate q_s
- symptomatic individuals are asked to isolate and do so effectively. **Model:** infectious individuals are moved to an isolated compartment at rate q_i

Stronger and weaker interventions

Stronger: 2-3 days to notify and isolate with these additional features

- ❑ Susceptible/exposed individuals are notified within **2 days**; over half are willing to reduce contact, with 35% effectiveness (q_s = 0.09 per day)
- ❑ Among those offered PEP, somewhat fewer accept it than isolate; q_{pep} = 0.06 per day. (Minnesota outbreak 2017)
- ❑ Within **0.5 to 1** day of rash onset, most individuals isolate with high effectiveness but this is imperfect (highly transmissible; household contacts; may seek healthcare). We use $q_i = 0.4$ (1 day x 40%, reflecting both some individuals not isolating and imperfect isolation).

Weaker: 4-5 days to notify and isolate with these additional features

- ❑ Susceptible/exposed notified within **4 days**; over half reduce contact 35% effective: q_s = 0.054
- ❑ PEP offered less because fewer exposed people are found soon enough: q_{pep} = 0.036 per day
- ❑ Within **1-2 days** of rash onset, most individuals with rash isolate as above: q_i = 0.24 per day

We note that without any interventions, under 90% vaccination coverage, essentially all non-immune individuals get measles.

Parameters: further discussion

qs: Rate at which those who have been exposed are removed from risk. Suppose it takes 2 days to find and contact susceptible people with exposure risk; if half of them do so immediately with approximately 35\% effectiveness we have an overall rate of 0.09 per day; if case finding and isolation are less rapid or effective we model this with qs=0.054 per day. Equivalently, if we took 4 days to find and contact people, and 75% of them do so immediately with 50% effectiveness we get approximately the same rate.
qs = {1/(time to contact) } { fraction who agree to reduce contact} {fraction of remaining contacts }

qpep: Rate at which infected individuals are removed from risk due to PEP. Two days to contact individuals, with partial uptake. We use a sum of qs and qpep for infected (pre-rash) individuals -- removing them from risk from a combination of isolation and PEP (qspep = qs + qpep)
qpep = { 1/ (time to contact)} {fraction offered PEP} {fraction who accept PEP if offered} { effectiveness of PEP}

In Minnesota, in a measles outbreak in 2017, just over 1/4 as many people received PEP as were excluded from childcare settings, though the denominators are not given. This suggests that the rates of PEP and isolation/exclusion do not differ by orders of magnitude and that the PEP rate is lower.

qi: Rate at which we remove infectious people with rash from infecting others.
qi: optimistically, within 0.5 to 1 day of rash onset, nearly half of individuals isolate with high effectiveness (being unable to avoid contact with their household, and given the highly transmissible and airborne nature of measles and the potential need to seek healthcare). This gives $q_i = 0.4$; if isolation is slower and/or less effective we model that with qi=0.24.

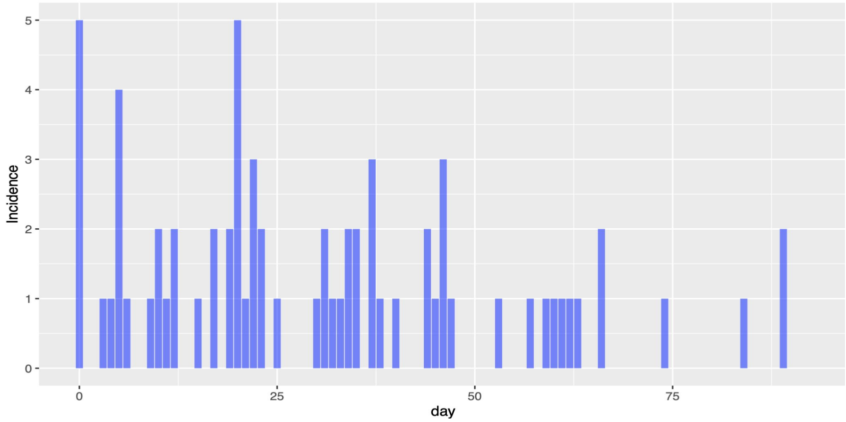
Table of parameters

Parameter	Value	Description	Note
R0	15	Basic reproduction number	Usually 12-18. WHO, CDC.
c	0.3	Fraction of pre-rash time when people are infectious (~4 days before rash)	Infectious 4 days before rash; duration pre-rash is 10 days, so this covers individuals that are not yet infectious at all, and those who are 4 days pre-rash.
v	0.005, 0.003 per day	Additional uptake of MMR during an outbreak	BC enhanced vaccination in 2019; rough estimate based on reported numbers of additional vaccines
qs	0.09, 0.054 per day	Reduced contact for susceptible individuals following exposure notifications	See notes on the previous slide
qspep	0.15, 0.09 per day	PEP rate + qs	See notes on the previous slide
qi	0.4, 0.24 per day	identification and isolation of infectious individuals with rash	See notes on the previous slide
(1/gamma)	4 days	duration of rash	WHO
(1/k)	10 days	time from infection to rash onset	WHO

Validation

- ❑ We aim to model realistic timing and behaviour. Parameters reflecting public health interventions are hard to estimate.
- ❑ Interventions control outbreaks if coverage is 75-80% or more, consistent with Canadian jurisdictions usually avoiding sizeable outbreaks when measles is introduced.
- ❑ Model outbreaks typically last 60-70 days, longer for larger outbreaks in larger populations. This is similar to reported outbreaks.
- ❑ The range of outbreak sizes (see below) is consistent with reported outbreaks.
- ❑ As with introductions to Canada, under higher vaccination coverage, most exposures do not result in an outbreak; transmission is not sustained.

Comparison: a simulated and a real outbreak



Example outbreak in the model. This is in the large population (8000) with strong public health interventions and 75% vaccination coverage. This particular outbreak had 69 cases

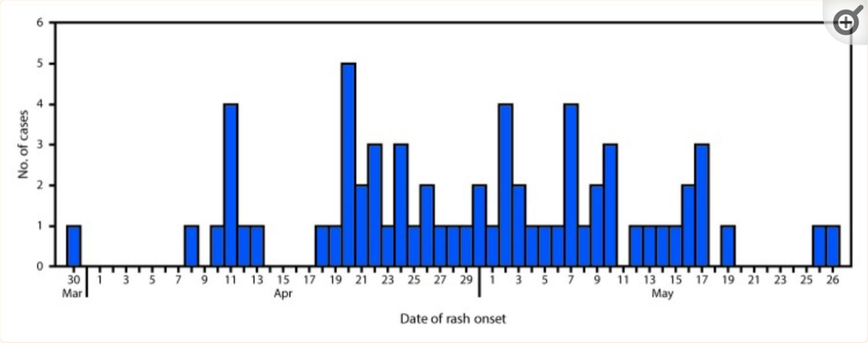


FIGURE 1

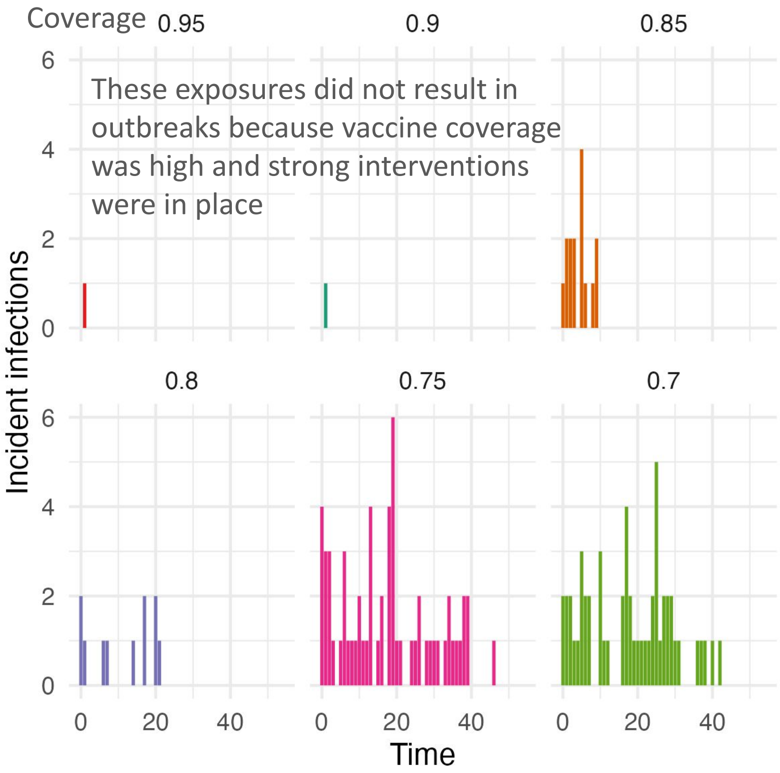
Number of measles cases (N = 65) by date of rash onset — Minnesota, March 30–May 27, 2017

The figure above is a histogram, an epidemiologic curve showing the 65 measles cases by date of rash onset in an outbreak in Minnesota during March 30–May 27, 2017.

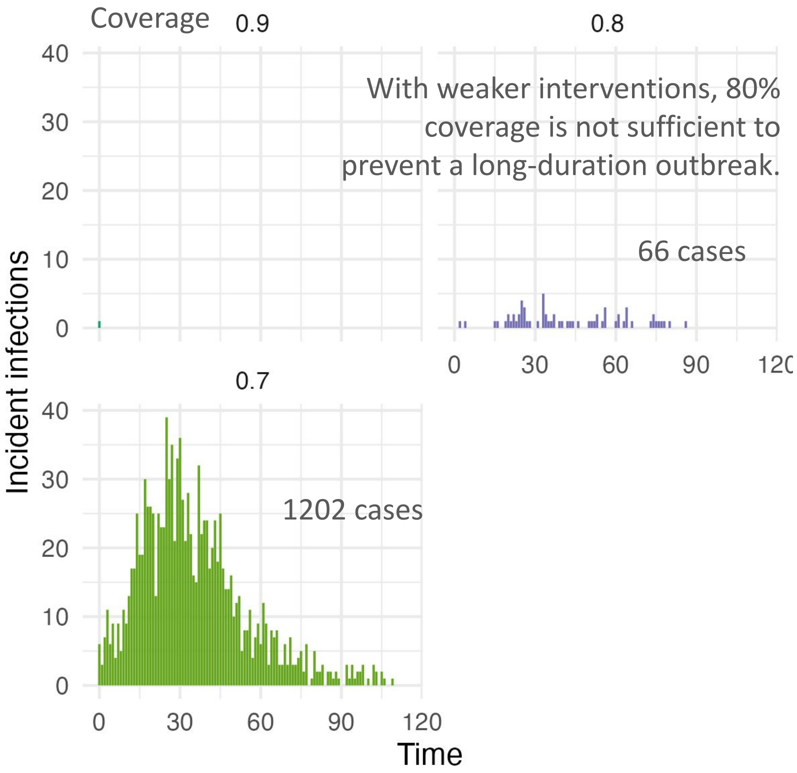
Hall et al, 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5687591
There were 8000 people potentially exposed. Interventions included case finding, isolation and PEP, in a partially vaccinated community

Example outbreaks (larger population of 8000)

Strong interventions



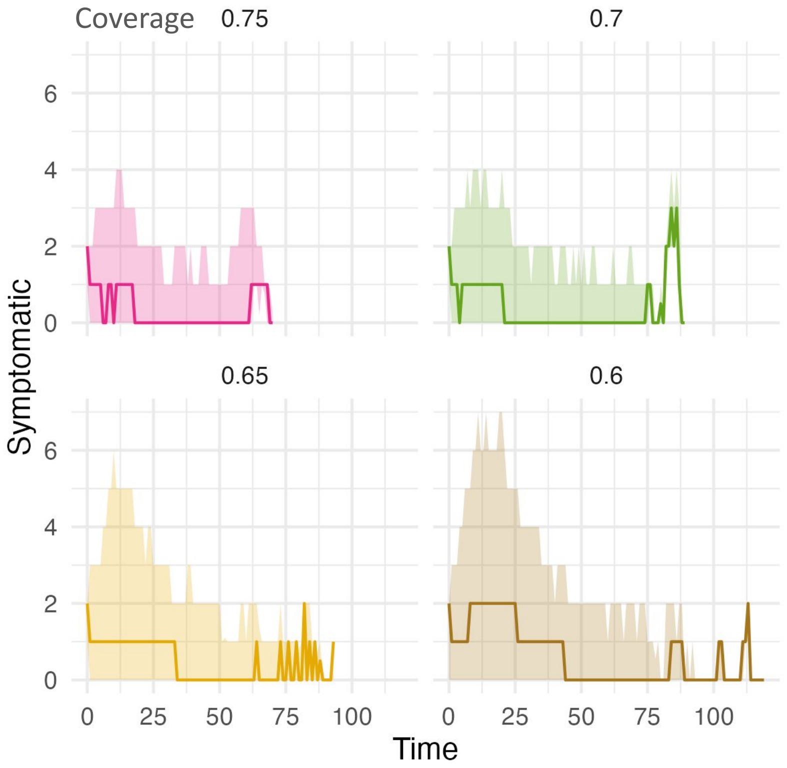
Weak interventions



Outbreaks in small population (1000), strong interventions

Plots show the 95% range for the number of individuals infectious with rash by vaccine coverage under the stronger public health interventions.

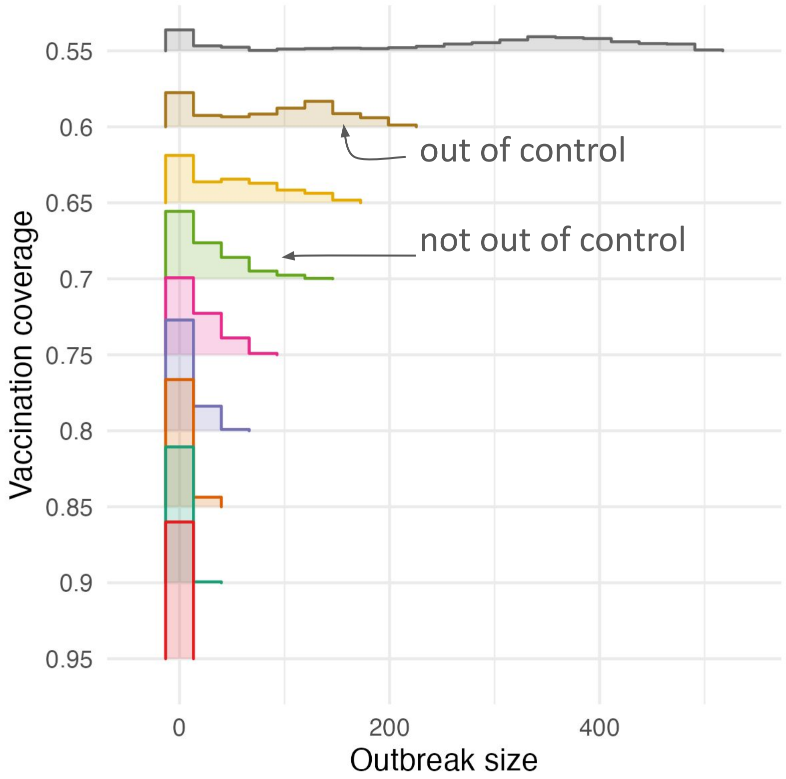
While control is good, stuttering transmission chains can last for months with 65% coverage



Outbreak sizes in the small population, strong interventions

These plots show the distribution of simulated outbreak sizes by vaccine coverage. While many exposures do not lead to outbreaks, the chance of a sizeable outbreak is high (above 50% with 70% coverage).

With 55-65% coverage, outbreaks are not well controlled. Sizes can reach in the 100s unless even further measures are taken.



Severe outcomes

Measles can cause severe outcomes; the risks vary by age. Overall, the CDC reports these risks (Perry et al 2004 and CDC):

- **Hospitalization** is required in 1 of 5 cases
- **Diarrhea** less than 1 of every 10 cases
- **Pneumonia** 1 of every 10 cases
- **Otitis media** 1 of every 10 cases
- **Death** is estimated to occur in 1 to 3 of every 1,000 cases of measles
- **Encephalitis** occurs in approximately 1 of every 1,000 reported cases

We compute the expected number of these outcomes for the median outbreak sizes in our simulations.

Outbreak sizes and expected numbers of severe outcomes

Small population, strong interventions

Vaccination coverage	Median outbreak size	5%	95%	Hospitalizations	Diarrhea/ Pneumonia/ Otitis media	Encephalitis	Death
0.95	0	0	3	0	0	0	0
0.9	1	0	7	0.2	0.1	0.001	0.002
0.85	2	0	15.05	0.4	0.2	0.002	0.004
0.8	5	0	27	1	0.5	0.005	0.01
0.75	10	0	53	2	1	0.01	0.02
0.7	14	0	78.05	2.8	1.4	0.014	0.028
0.65	39.5	0	127.1	7.9	3.95	0.0395	0.079
0.6	92.5	0	182.05	18.5	9.25	0.0925	0.185
0.55	323	0	468	64.6	32.3	0.323	0.646

Median and quantiles for the outbreak size, and expected numbers of various outcomes at the median outbreak size, given reported risks of these outcomes (CDC). **Note:** risks for this table are per *reported* case. We assume complete ascertainment. If some transmission is in undetected cases who acquire immunity, these numbers would be lower. **Note:** Age matters, as risks vary by age. Numbers are overall rates because we do not know the age demographics or contact patterns in the relevant communities.

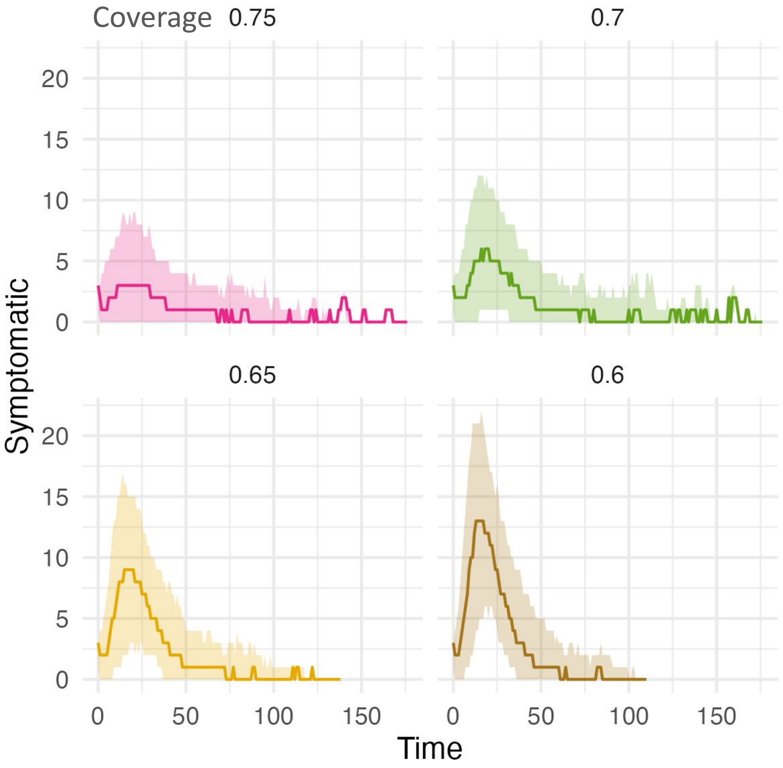
What happens with milder interventions?

Small population (1000), weaker interventions

Plots show the 90% range (5-95% quantile) for the number with rash, by vaccine coverage, under the weaker interventions (less effective case finding and isolation, reduced PEP uptake)

When coverage is 0.75, transmission can be ongoing at low levels for a considerable time.

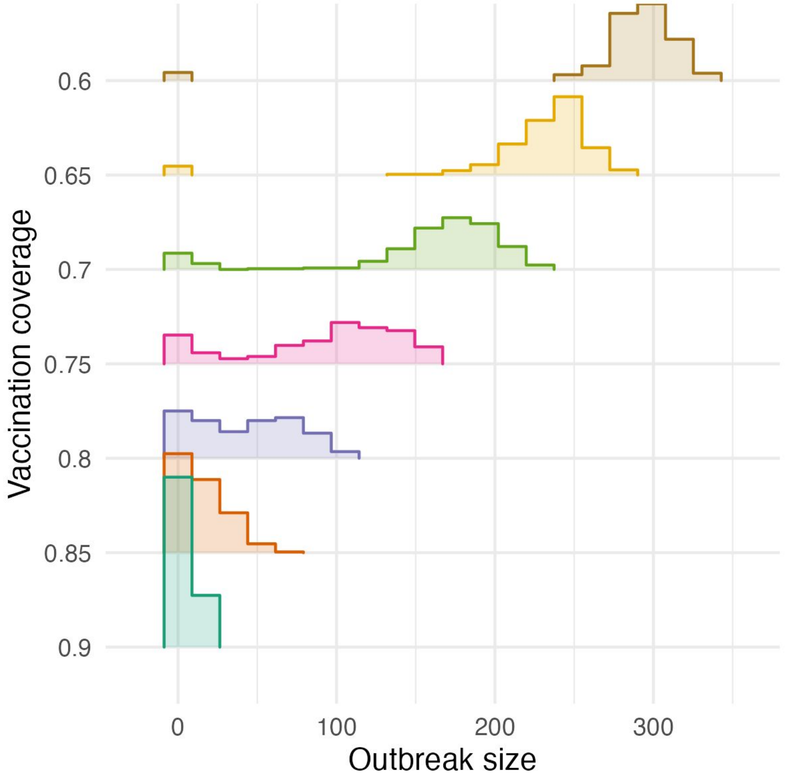
At lower coverage, outbreaks are sizeable and have long duration.



Outbreak sizes: small population (1000), weaker interventions

These plots show the distribution of outbreak sizes under the weaker interventions.

When coverage is lower than 0.85, outbreaks frequently have over 50 cases, and with lower coverage, go up to hundreds of cases.



Outbreak sizes and expected numbers of severe outcomes

Small population, weaker interventions

Vaccination coverage	Median outbreak size	5%	95%	Hospitalizations	Diarrhea/ Pneumonia/ Otitis media	Encephalitis	Death
0.9	3	0	16.05	0.6	0.3	0.003	0.006
0.85	11	0	41	2.2	1.1	0.011	0.022
0.8	43	0	91	8.6	4.3	0.043	0.086
0.75	103	0	155	20.6	10.3	0.103	0.206
0.7	172	2.95	209.05	34.4	17.2	0.172	0.344
0.65	237.5	173.85	265.05	47.5	23.75	0.2375	0.475
0.6	295	249.9	323.05	59	29.5	0.295	0.59

Median and quantiles for the outbreak size, and expected numbers of various outcomes at the median outbreak size, given reported risks of these outcomes (CDC). **Note:** risks for this table are per *reported* case. We assume complete ascertainment. If some transmission is in undetected cases who acquire immunity, these numbers would be lower. **Note:** Age matters, as risks vary by age. Numbers are overall rates because we do not know the age demographics or contact patterns in the relevant communities.

Results: large population (8000), strong interventions

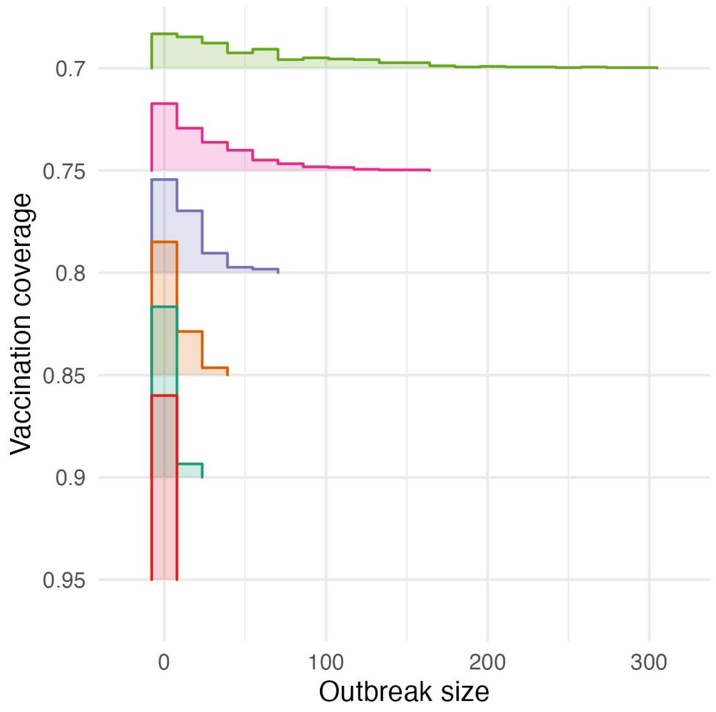
Outbreak size distributions in the large population.

Now even at 70% vaccination there can be 100s of cases, but these are still “controlled” (the number of cases is much smaller than the number unvaccinated).

With lower coverage there are much larger outbreaks, even with “strong” interventions:

- 1000 cases at 60% coverage
- 2800 cases at 55% coverage

The number of expected severe outcomes scales accordingly, proportional to the size, though the age distribution matters.



Selected limitations

- The model is simple - no age structure, simple mixing, constant rates.
- Information about age-based contact during outbreaks is not available. Contact patterns change during outbreaks in response to exposure, public health messaging, interventions and community response. The risk of more severe outcomes also differs by age. Vaccine coverage varies by age
- It is challenging to translate interventions to model parameters.
- Past reported outbreaks are highly variable (as are simulated outbreaks); hard to validate.
- We have mostly modelled a small social network or community of 1000 people. Results (including outbreak size) when outbreaks are well controlled are consistent in larger populations.
- The size of outbreaks when they are not well controlled is much larger in larger populations.
- We assume high reporting. In Lyon, France, where there was a very large outbreak, reporting was thought to be closer to 50% . In our model under-reporting is partially accounted for with incomplete test, trace and isolate, but our outbreak sizes include all infections.
- Outbreak sizes are inherently unpredictable, but we can characterize risks of larger outbreaks at varying coverage levels, along with their timing and size distribution

Conclusions

- There is a global measles outbreak and Canadian jurisdictions are likely to see more introductions.
- Measles can spread in some Canadian settings, due to lower vaccination coverage.
- When introductions occur in these settings, outbreaks can reach dozens to hundreds of cases and require strong or very strong public health interventions to control.
- Transmission chains can last for months at low levels. This presents the risk that outbreaks will be viewed as over if cases are missed, and that new settings could be exposed.
- Outbreaks are unpredictable and sizes are variable, but we can characterize risks of larger outbreaks and project their potential sizes and durations in different communities.

Thank you

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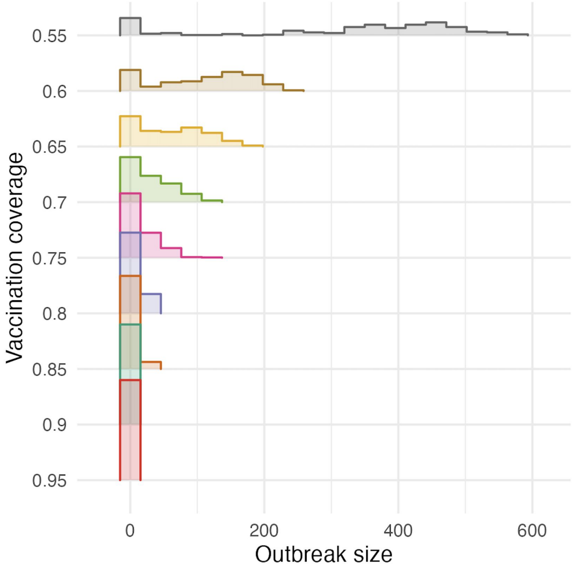
CANMOD
Canadian Network for Modelling Infectious Diseases
Réseau canadien de modélisation des maladies infectieuses

SFU SIMON FRASER UNIVERSITY
DEPARTMENT OF MATHEMATICS

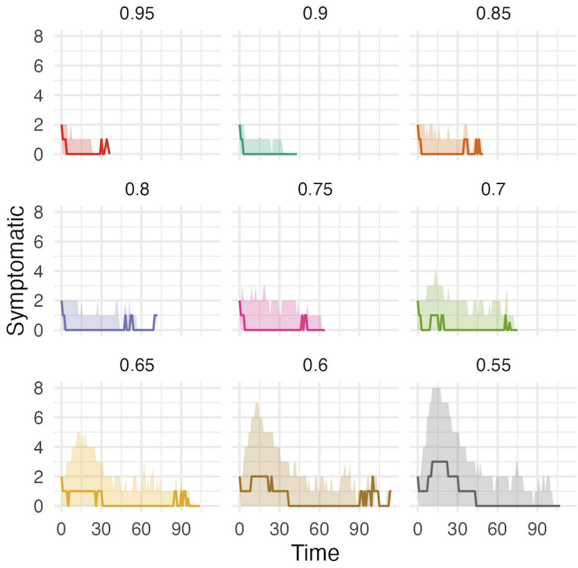
Small population, stronger measures, alternative parameters

Strong: 2-3 days to notify; half eligible for PEP, 90% choose PEP and it's 70% effective PLUS the other half that are not eligible for PEP: half of them reduce contact to protect others, and they do so by reducing 35% of their (close enough for measles) contacts

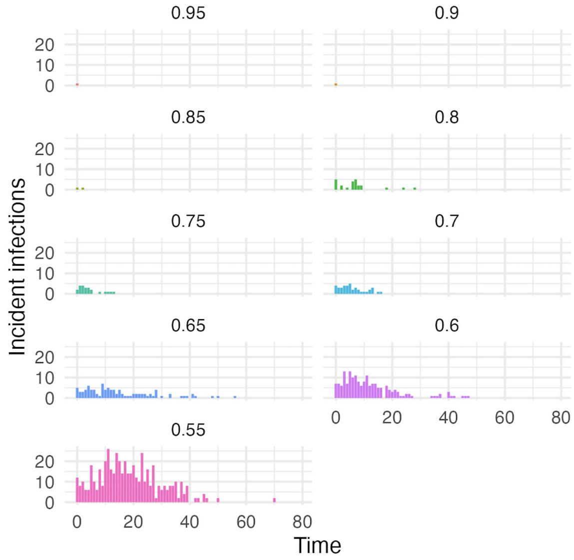
Outbreak sizes



Median and range



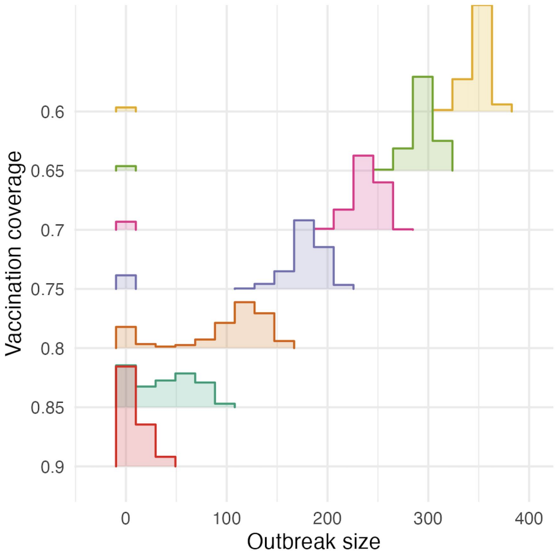
Example outbreaks



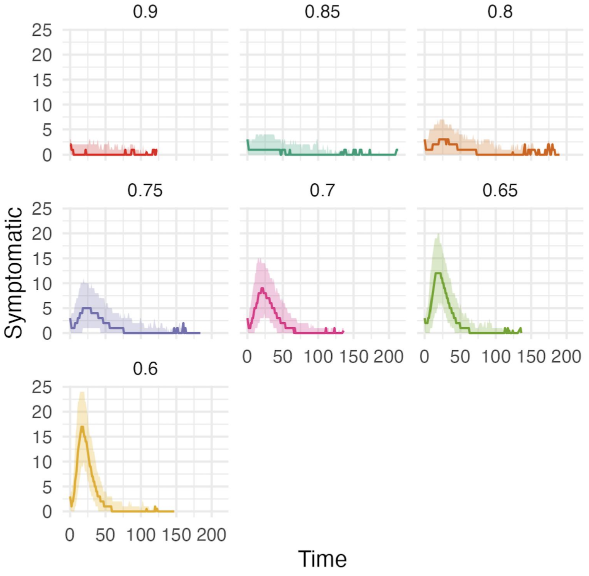
Small population, weaker interventions, alternative

Weak: 4-5 days to notify; 1/4 are eligible for PEP, 90% choose PEP and it's 60% effective, PLUS the other 3/4 that are not eligible for PEP: half of them reduce contact at a 35% reduction in contact

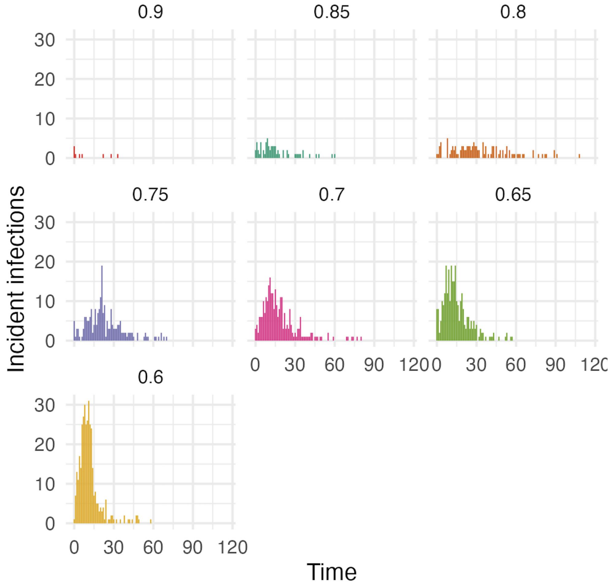
Outbreak sizes



Median and range

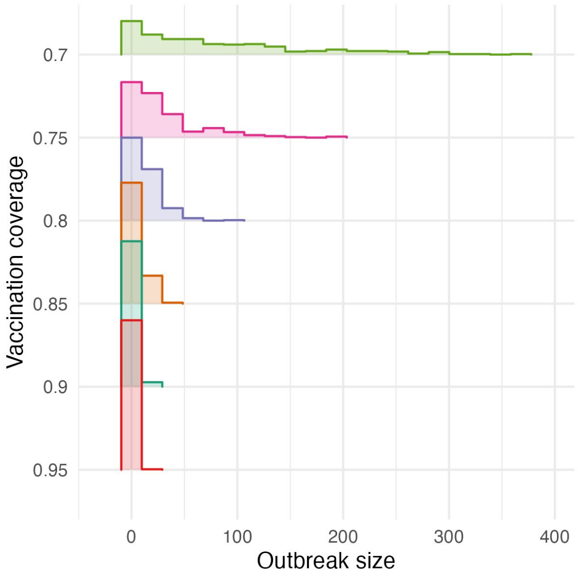


Example outbreaks

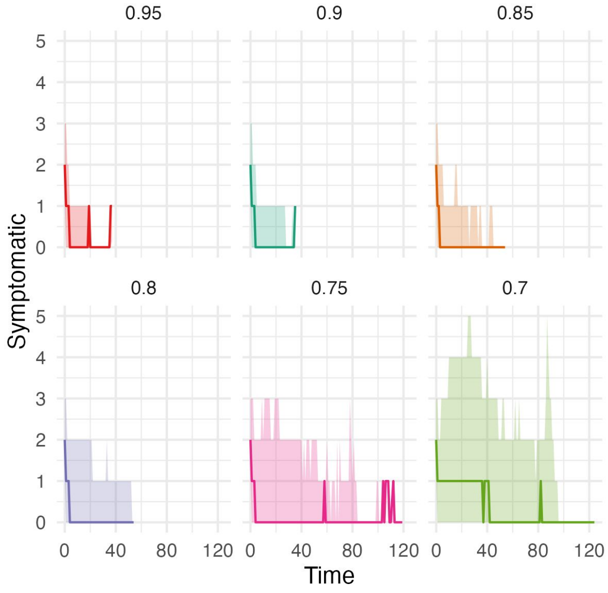


Large population, strong measures, alternative parameters

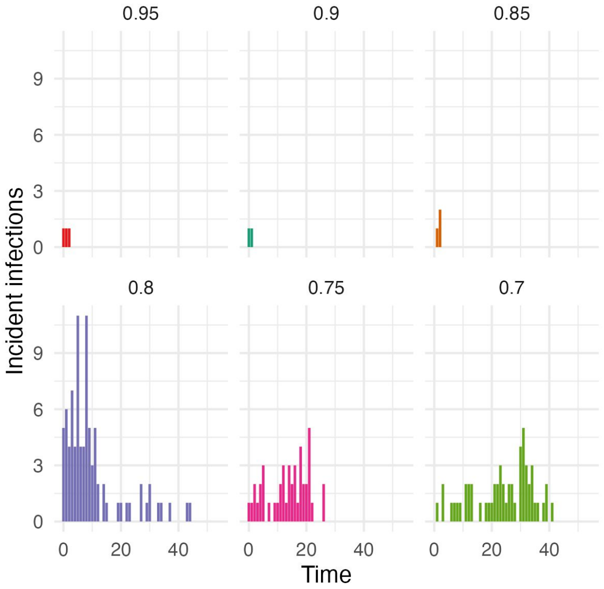
Outbreak sizes



Median and range

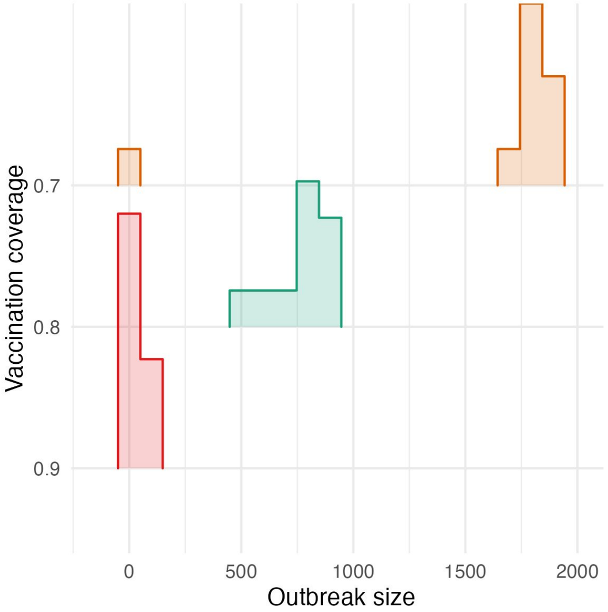


Example outbreaks

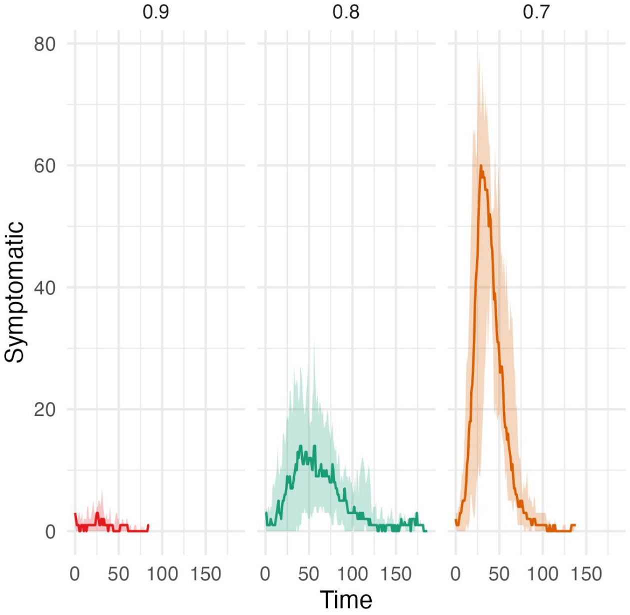


Large population, weak measures, alternative parameters

Outbreak sizes



Median and range



Example outbreaks