Modelling emerging viral threats

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Background

- Communicable diseases are unique because they have the capacity to be transmitted (from human to human or animal to human)
- Humans exist in mutually exclusive states of susceptibility, infection or immunity.
- Potential for epidemics
- Immunity results from natural infection OR vaccination

Risk factors

- Socioeconomic factors
  - Crowding
  - Sanitation
  - Potable water
  - Immunisation rates
- Environmental
- Sexual behaviour
- Immunity

Disease control

- Prevention of infection
  - Surveillance and early warning
  - Vaccination
  - Quarantine
  - Prophylaxis (Antibiotics, antivirals, condoms)
- Control of established infection
  - Outbreak investigation
  - Antibiotics and antivirals (treatment to reduce infective period)
  - Vaccines
  - Isolation
  - Hospital infection control
  - Contact tracing

SPECIAL REPORT

The Neglected Dimension of Global Security — A Framework for Countering Infectious-Disease Crises

Peter Sands, M.P.A., Carmen Mundaca-Shah, M.D., Dr.P.H., and Victor J. Dzau, M.D.

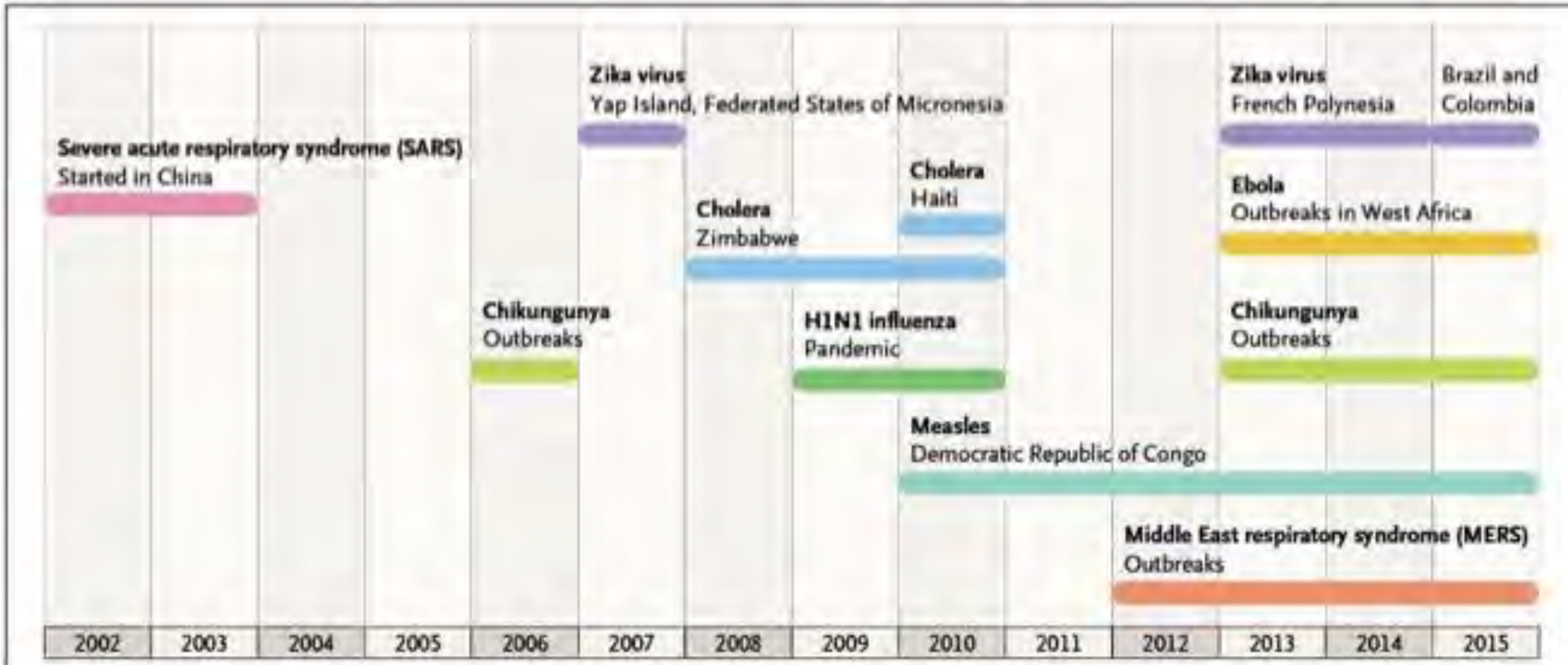
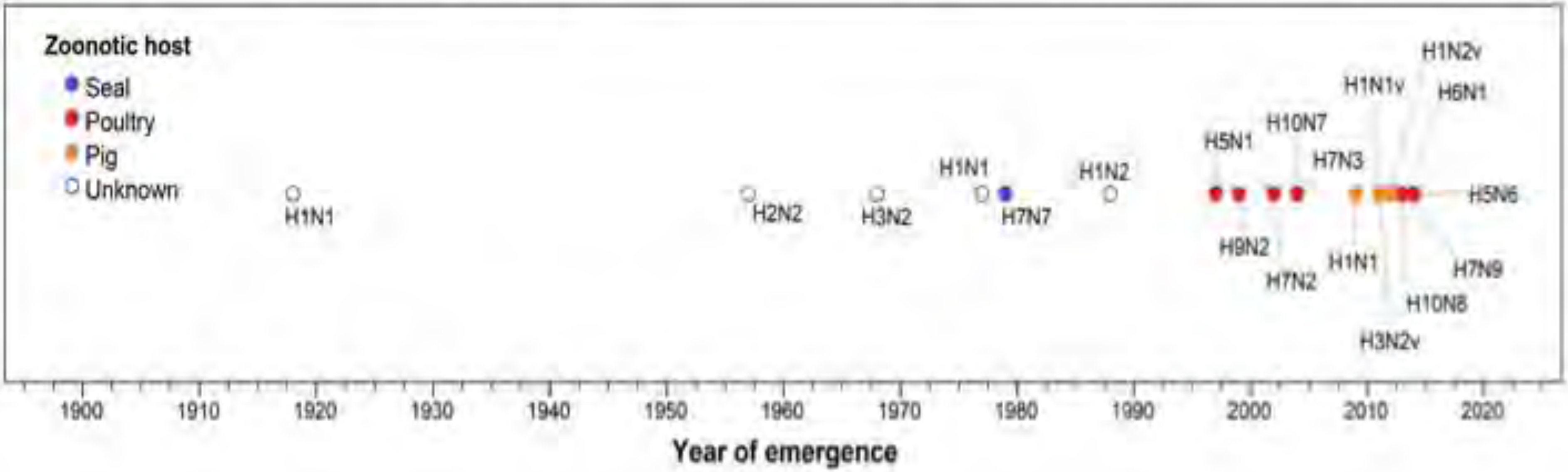


Figure 1. Major Emerging and Reemerging Infectious-Disease Outbreaks, Epidemics, and Pandemics, 2002 through 2015.

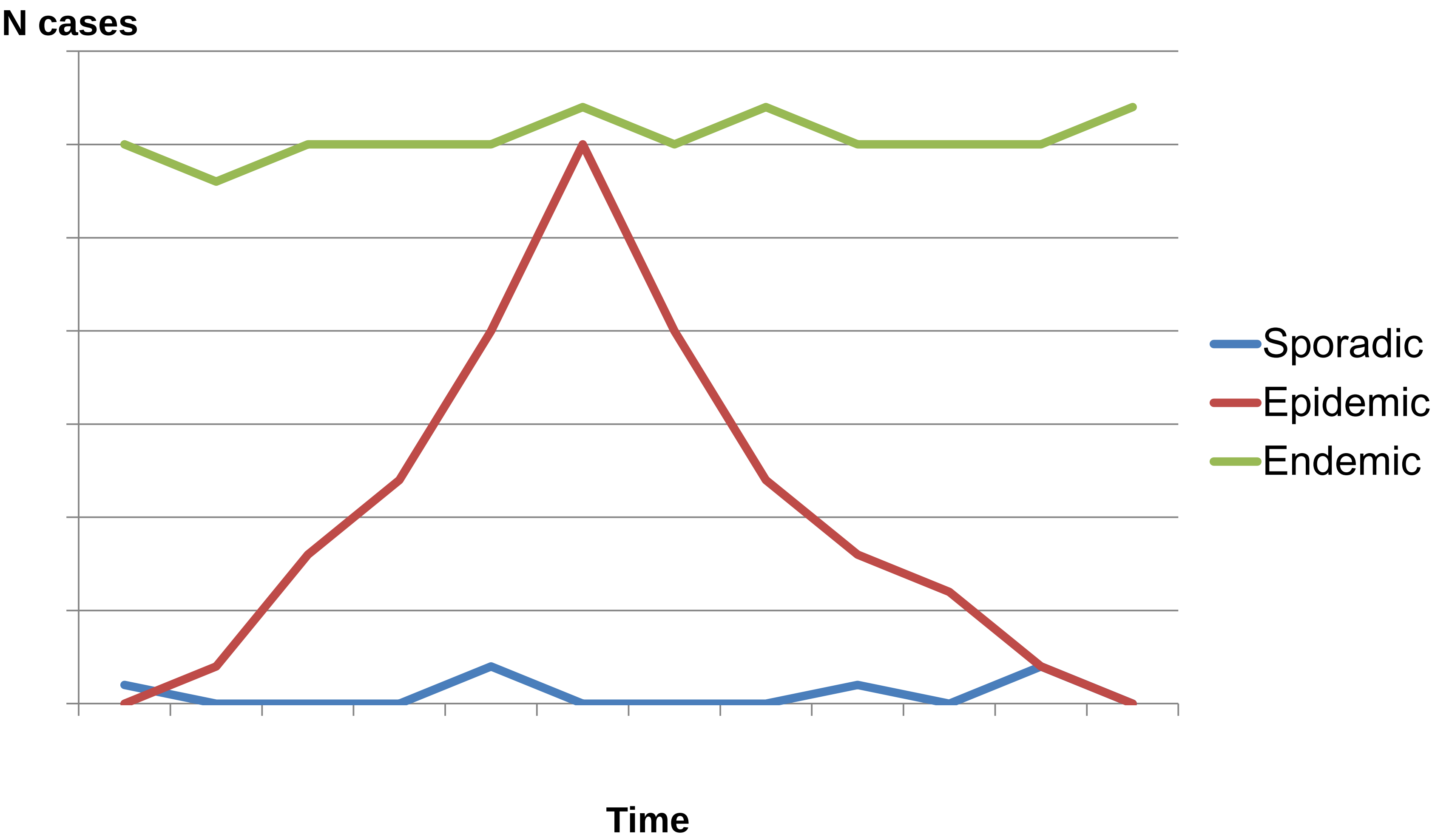
N Engl J Med 2016; 374:1281-1287March 31, 2016

Figure 1: Timeline of Influenza A serotype emergence in humans by year and zoonotic host from 1918 to 2015

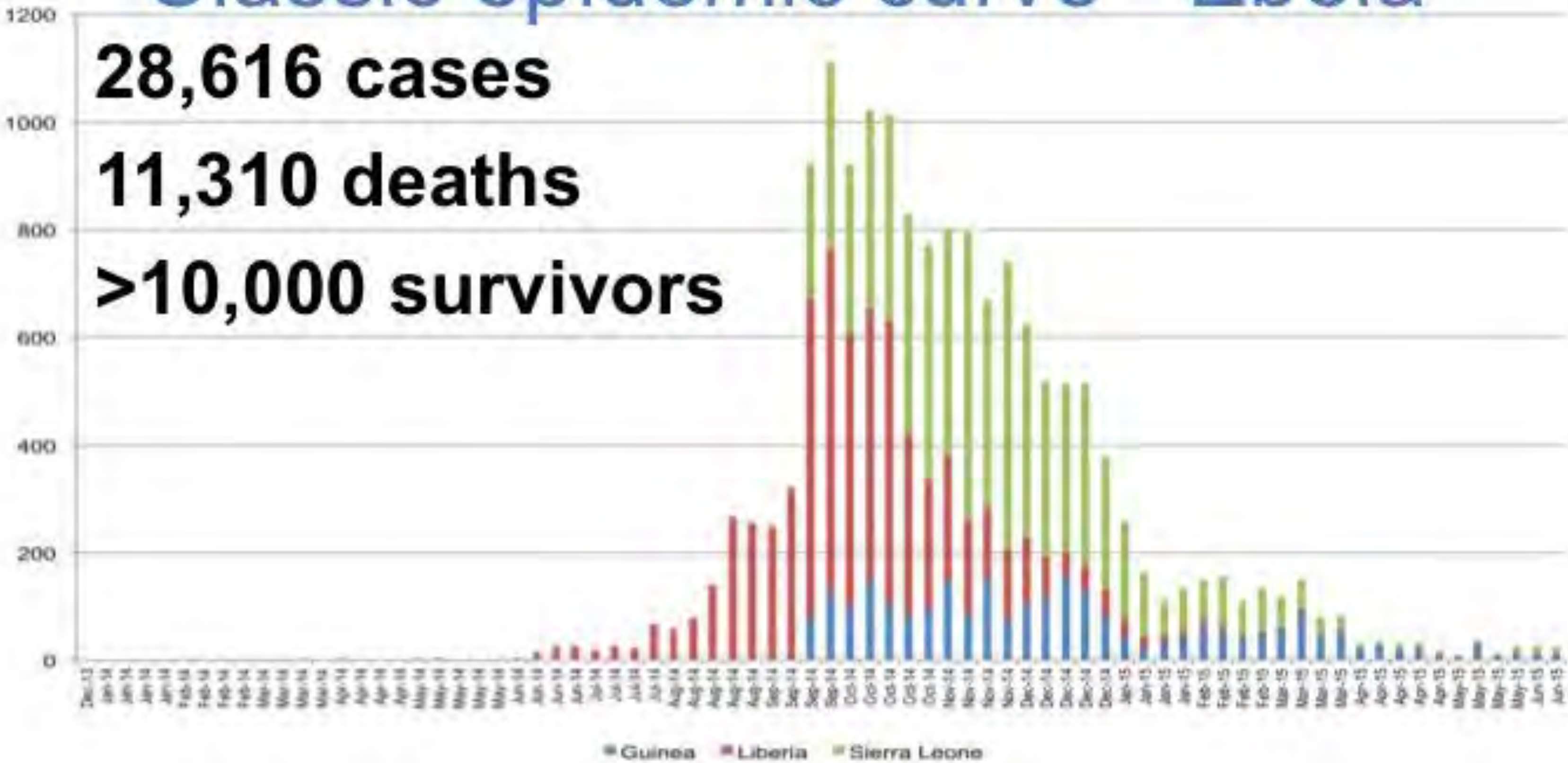


Chau Bui, et al. http://archpublichealth.biomedcentral.com/articles/10.1186/s13690-017-0182-z

Patterns of disease



Classic epidemic curve - Ebola



Data source: WHO

Not an epidemic

- Diabetes
- Heart disease
- HIV
- Malaria
- Ice
- Obesity
- Cancer


The Sydney Morning Herald NSW

NOOSA

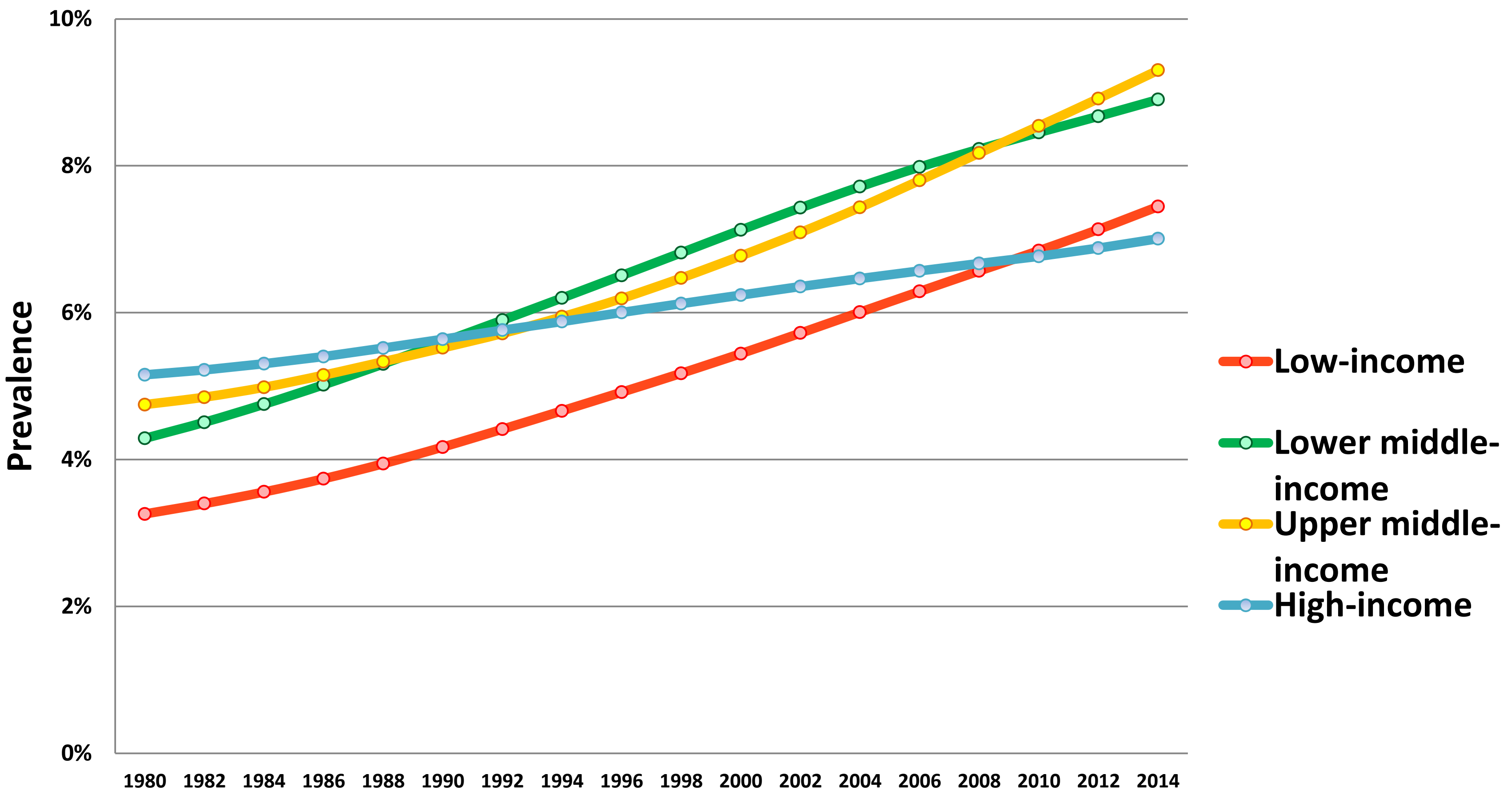
The diabetes epidemic: Up to half a million Australians have this deadly disease without realising it

Anna Patty and Inga Ting

Do you often find yourself thirsty? Tired? Any darkened spots on your skin, or a bruise that just won't seem to go away?

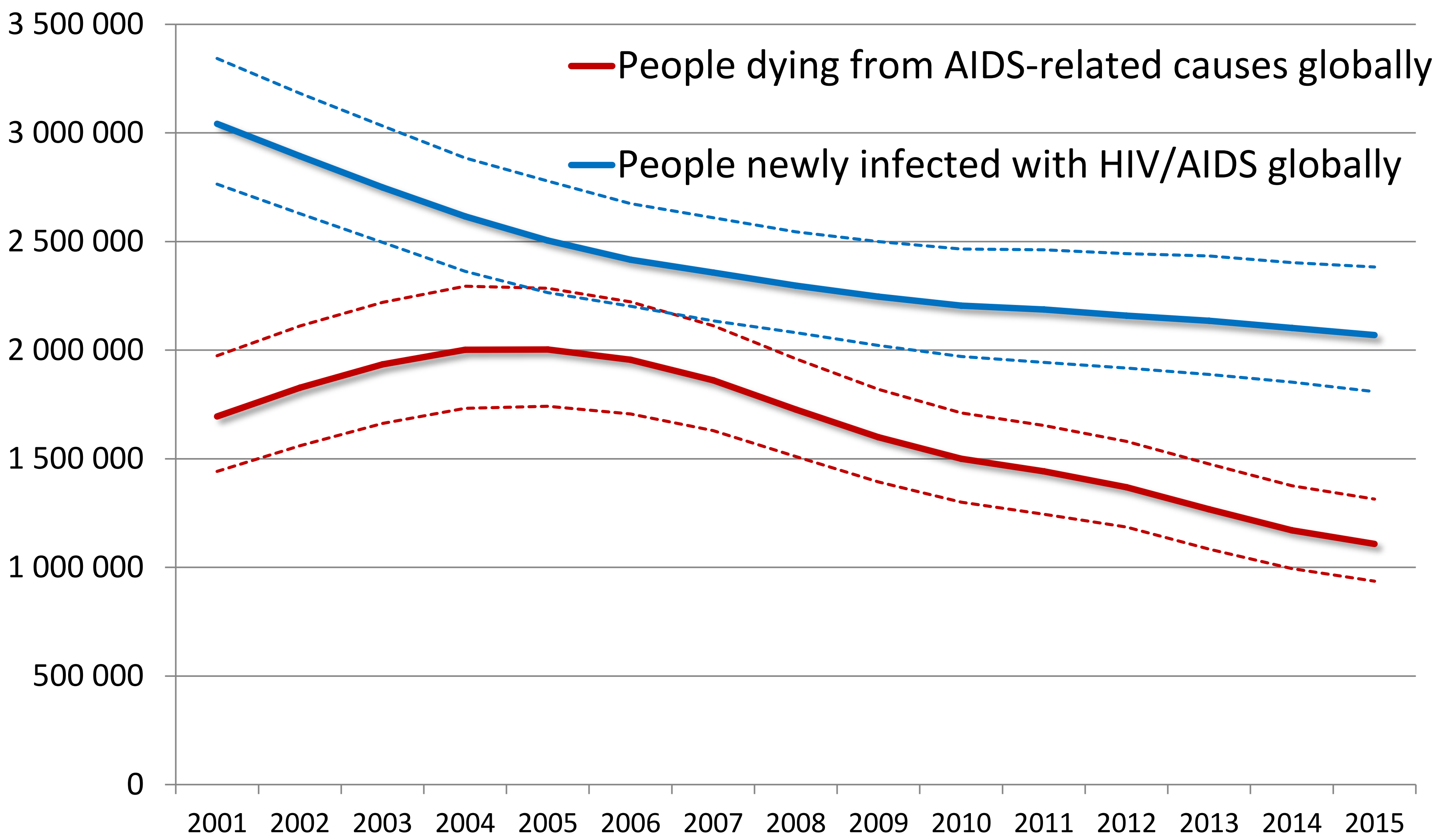
You may have diabetes and not know it.

Diabetes - rise is faster in low- and middle - income countries



Source: WHO estimates http://www.who.int/diabetes/global-report/en/

Decline in HIV incidence and mortality over time



Source: UNAIDS/WHO estimates http://www.who.int/hiv/pub/progressreports/2016-progress-report/en/

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A little bit of EBM is a dangerous thing

Research question: *Does smoking cause lung cancer?*

Answer: "*I couldn't find a meta-analysis or even a single RCT, therefore the level of evidence is low and I don't know if smoking causes lung cancer*."

Research question: *Is school closure effective in a pandemic?*

Answer: *"I couldn't find a meta-analysis or even a single RCT, therefore the level of evidence is low and I don't know if school closure if effective."*

Levels of Evidence….

Are specific to types of research questions
(http://www.cche.net/usersguides/main.asp)

Research questions can be about:

- Therapy
- Screening
- Diagnostic tests
- Aetiology
- Harm
- Prevention
- Prognosis
- Cost-effectiveness
- Future events
- etc

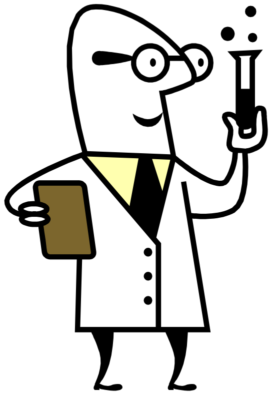
Modelling

- Disease or economic modelling
- The use of mathematical models to predict the dynamics, behaviour or economics of infectious diseases
- Useful when prediction of future outcomes and impact of control strategies is needed
- When an RCT is not possible because the disease of interest that you wish to prevent or treat has not yet occurred
- Useful for policy, planning or funding decisions

Isn’t surveillance enough?

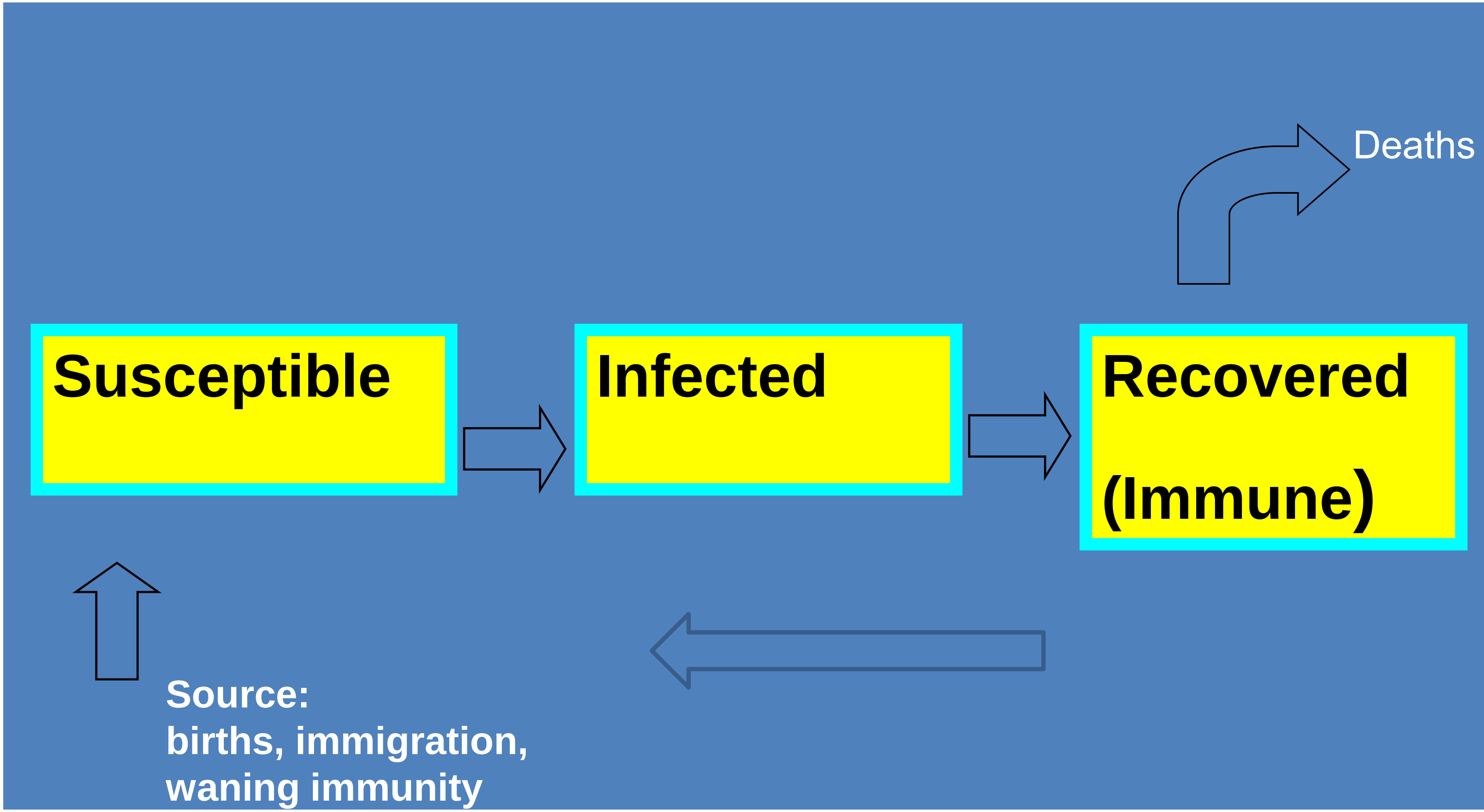
- Surveillance is based on past data and gives static/2-dimensional results
- Modelling allows forecasting
- Gives dynamic picture

What data are required?



- seroepidemiologic data (serosurveys)
- (enhanced) surveillance data
- disease transmission data
- vaccine coverage data (ACIR)
- vaccine or drug efficacy estimates (clinical trials)
- Cost data
- Travel, transport, social network data
- Geospatial data

Simple compartmental model



The meaning of R

R - the n of secondary cases generated from one index case

The lower the Ro, the easier it is to eradicate or control a disease

Factors affecting Ro

Characteristics of the organism

– Infectivity of organism

– Duration of infectiousness

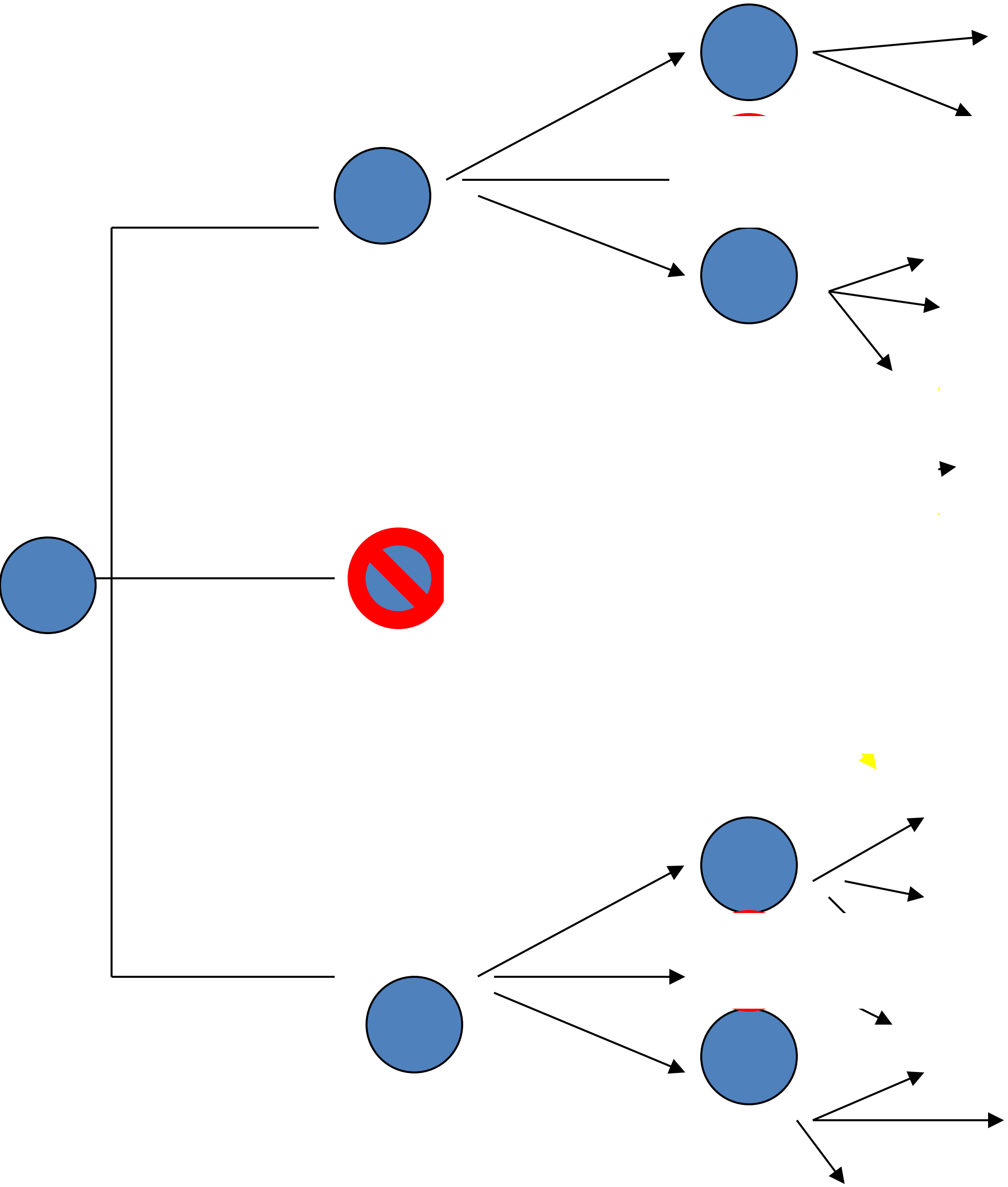
– Asymptomatic transmission

Population characteristics

– Demographics

– Social mixing patterns

– Population density



Examples of R

Pertussis	16-18
Measles	13-18
Mumps	11-14
Varicella	7-12
Rubella	6-10
Ebola	2-10
Influenza	2
Scarlet fever	5-8
Polio	5-7
Diphtheria	4-5
HIV	2-5 (men who have sex with men in UK)
	10-12 (heterosexuals in Uganda and Kenya)

Interpreting R

If R>1 the number of cases increases (an epidemic will occur)

If R<1 the number of cases decreases (infection cannot be sustained and dies out)

R=1 is the epidemic threshold

Questions suitable for modelling

- Forecasting/predicting epidemics
- Determining characteristics of a new emerged infection
- Testing impact of interventions
- Testing competing intervention options
- Risk analysis

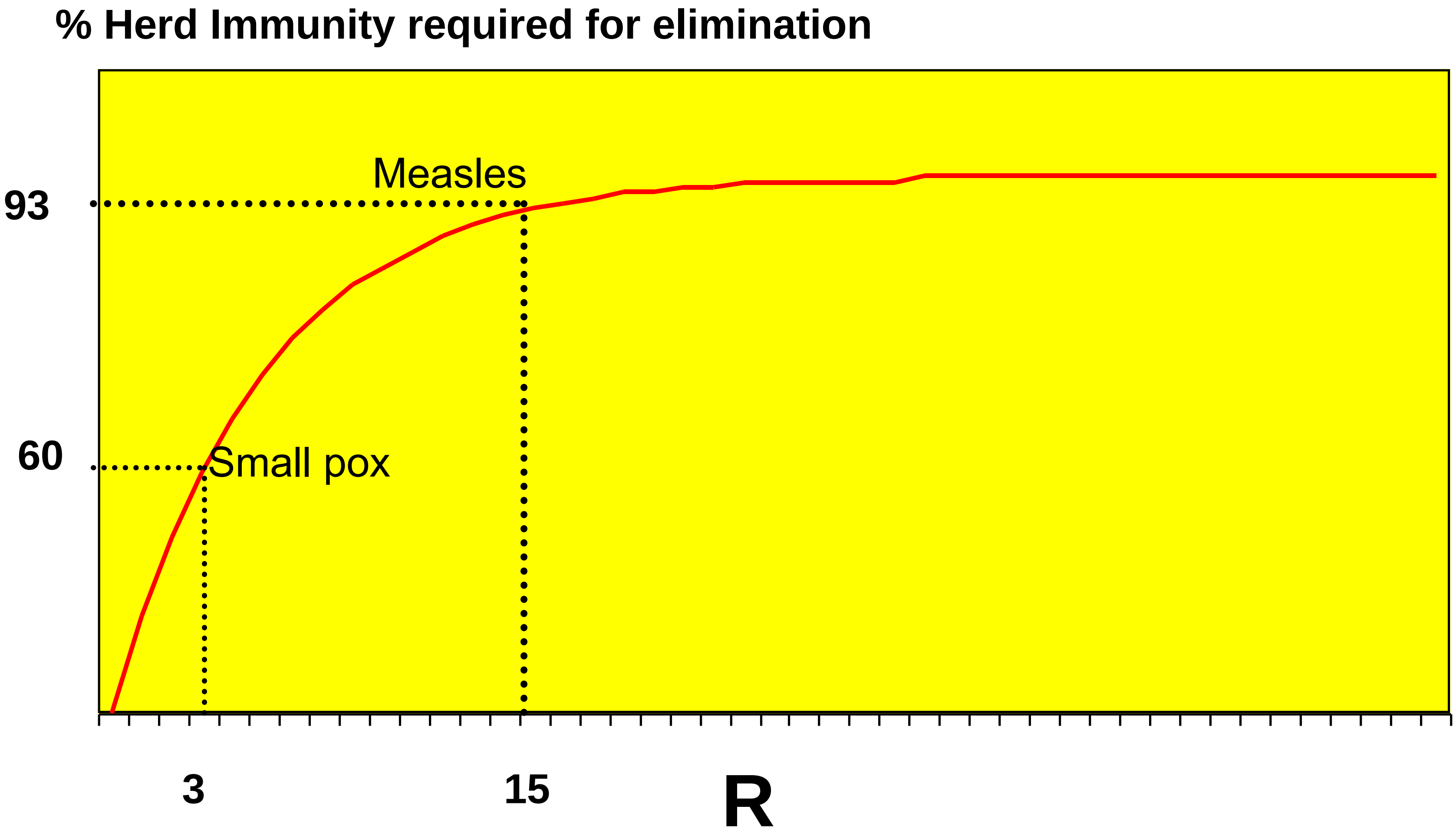
Special issues for vaccination

- Changes in disease epidemiology (R-shift of age specific incidence)
- Herd immunity
- Cross-protection
- Strain replacement
- Super-infection

Herd immunity

- A case of infection gives rise to a number of secondary cases (="R", the reproductive number). If the average R falls below one, then an outbreak will die out.
- Herd immunity is when the entire population is protected, whether they have been immunized or not, because the number of susceptible individuals is too small for infection to spread.
- Herd (H) immunity is a function of R; $H=1-(1/R^0)$
- Herd immunity relates mostly to infections of humans. Vaccinating enough of the population for a given disease (depending on the R for that disease), results in herd immunity. The higher the R, the higher the herd immunity required to control disease.

Elimination graph



Impact of vaccination

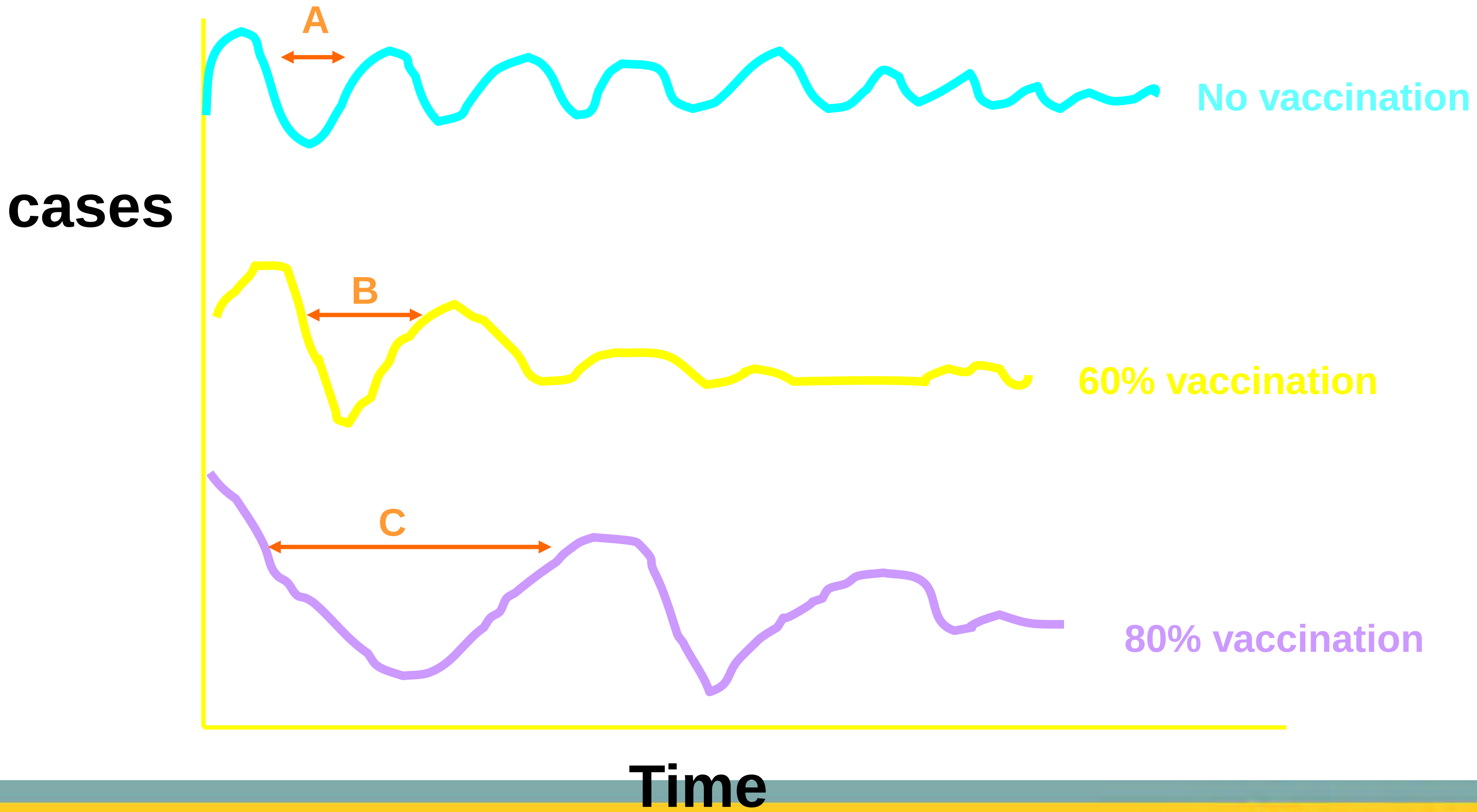
Reduction in number of cases

- reduced risk of infection
- increasing susceptibility in older age groups
- increased age at infection

Reduced input of susceptibles into population

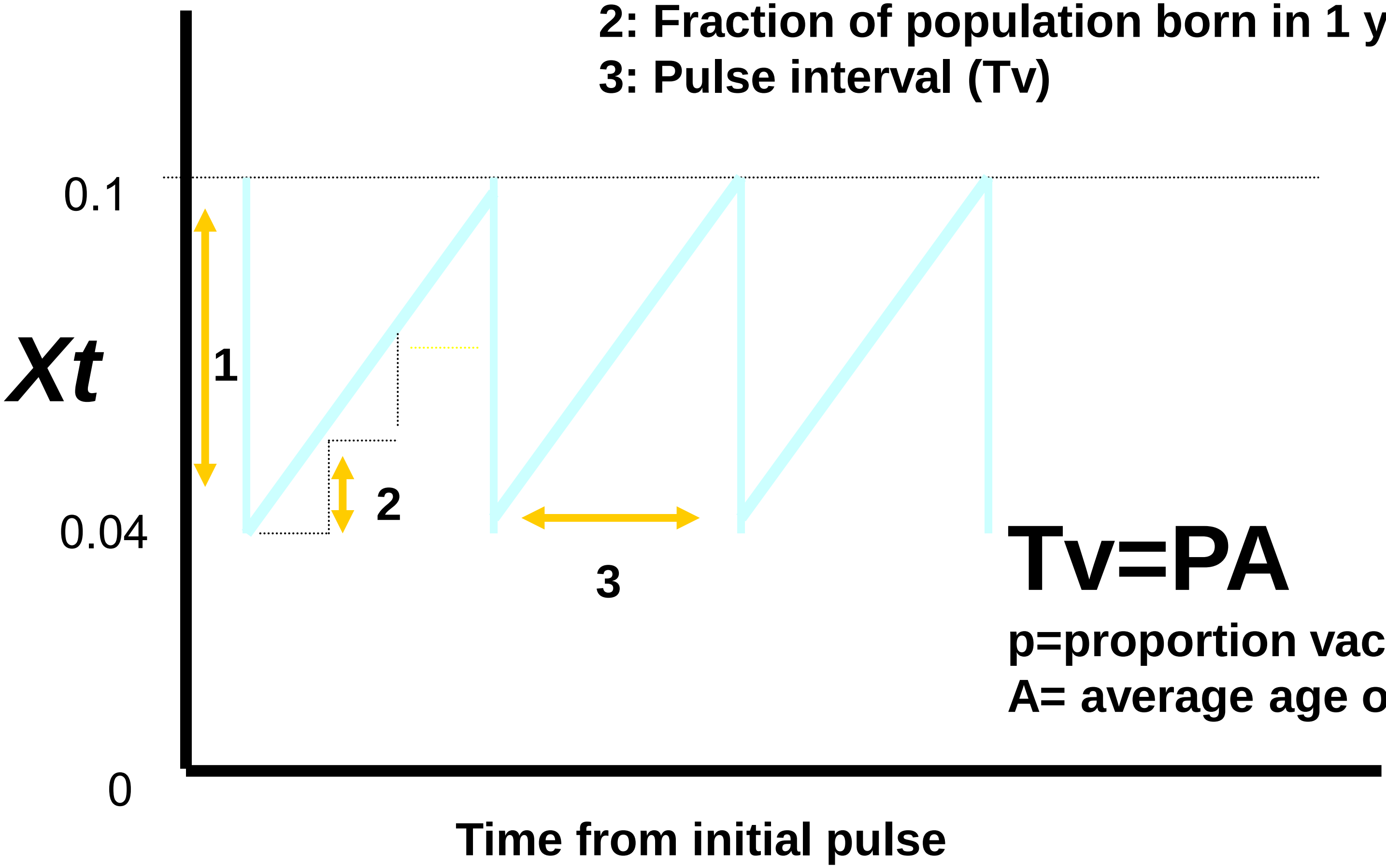
- lengthening of epidemic cycle

Impact of vaccination on disease incidence



Logic of pulse vaccination

1: Proportion vaccinated in 1 pulse
2: Fraction of population born in 1 yr
3: Pulse interval (Tv)



Tv=PA

p=proportion vaccinated
A= average age of infection

Measles in the Netherlands

Van den Hof et al, Epid & Infect 2002; 128:47-57

- National coverage 94-96% - schedule 14m, 9yrs
- Some municipalities as low as 53%
- Recurrent epidemics of measles (3293 cases in 2000), mostly in unvaccinated conscientious objectors
- However, 3% of cases in infants of “vaccine acceptors” too young for vaccination
- ?Best strategy to protect infants of vaccine acceptors in pockets of low coverage

Vaccine and age at vaccination

Measles	First MMR	Second MMR	% Susceptible (95% CI)	Rate of cases reported (year^{-1})†	% Lifetime spent susceptible (95% C
6 months	14 months	4 years	0·53 (0·31–0·63)	24	0·95 (0·59–1·07)
6 months	14 months	9 years	0·74 (0·37–0·89)	80	1·09 (0·64–1·26)
9 months	14 months	4 years	0·75 (0·55–0·84)	25	0·68 (0·54–0·75)
9 months	14 months	9 years	0·96 (0·60–1·10)	81	0·70 (0·54–0·78)
	11 months	4 years	0·95 (0·76–1·04)	26	1·09 (0·80–1·20)
	11 months	9 years	1·16 (0·81–1·31)	83	1·43 (0·92–1·61)
	14 months	4 years	1·27 (1·08–1·37)	34	1·27 (1·08–1·37)
	14 months	9 years	1·48 (1·13–1·63)	90	1·48 (1·13–1·63)

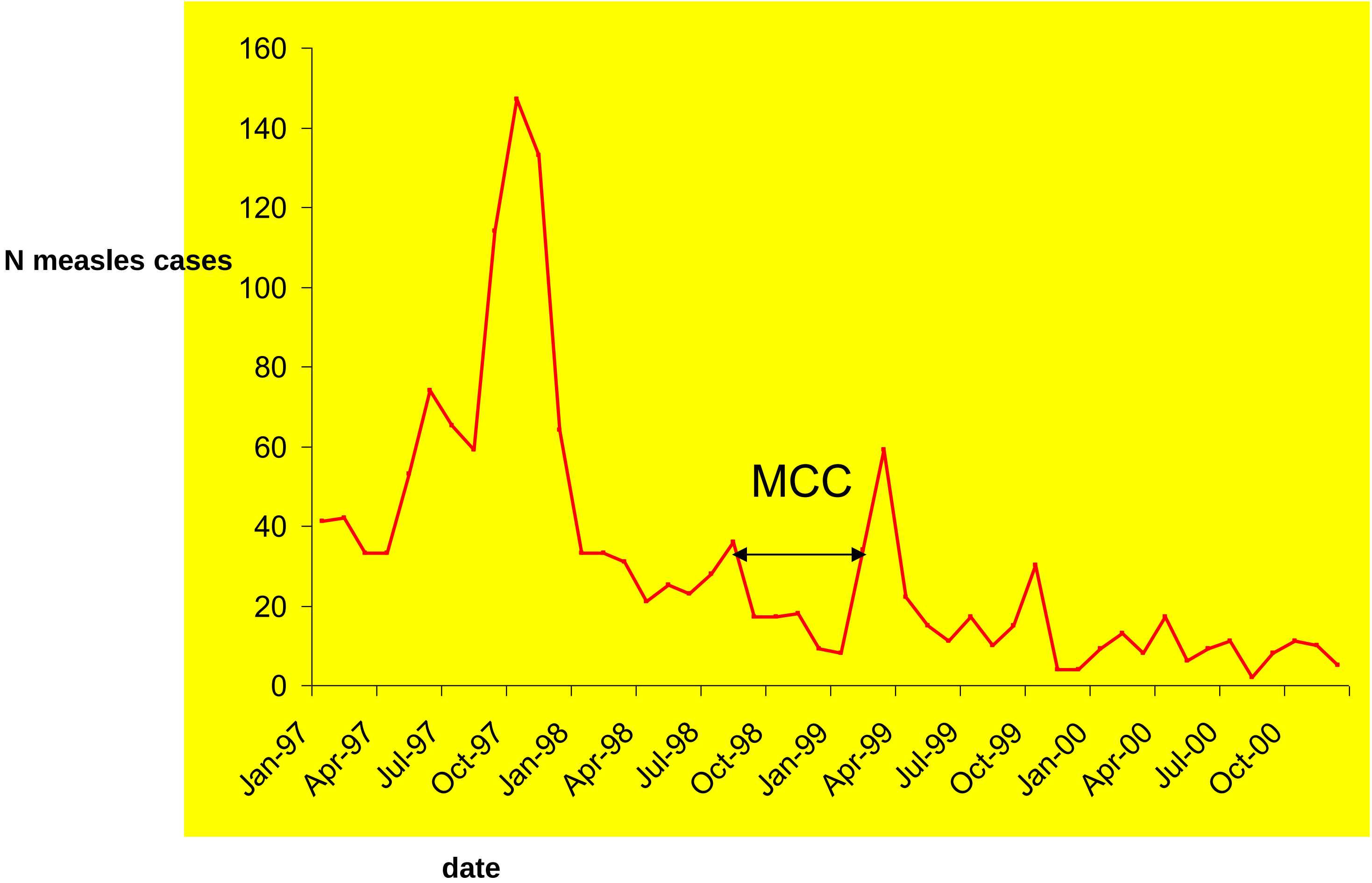
* Note that vaccine accepting population also includes infants too young to be vaccinated.

† Note that 1 reported case may stand for 40–70 real cases (see reference 14).

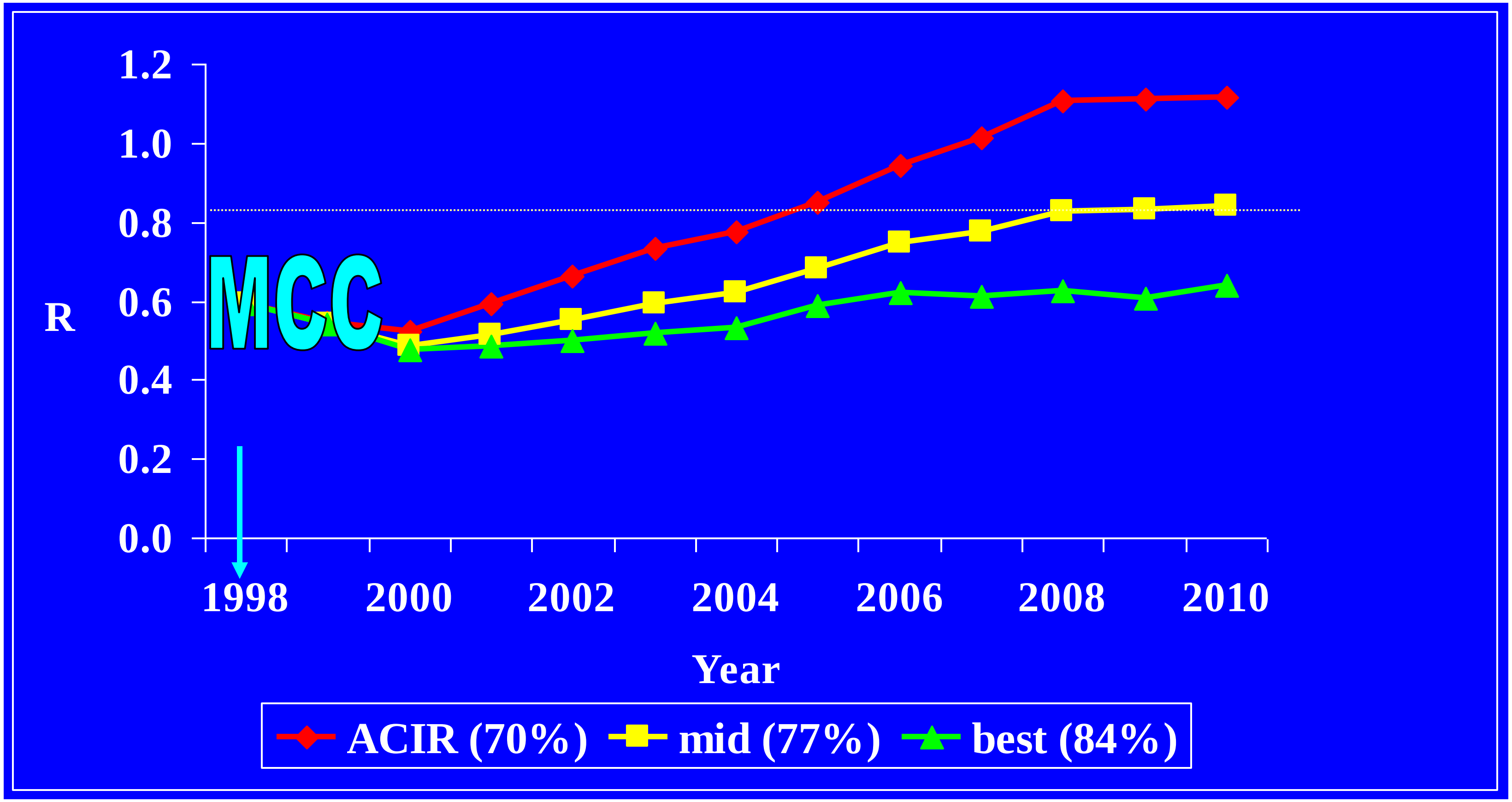
Measles control in Australia

- A mathematical model, using serosurvey results & ACIR coverage data, was used to calculate the change in R, the reproductive number, pre- and post MCC.
- ACIR coverage data used as "worst case scenario" and compared to ideal coverage levels ("best case" scenario).

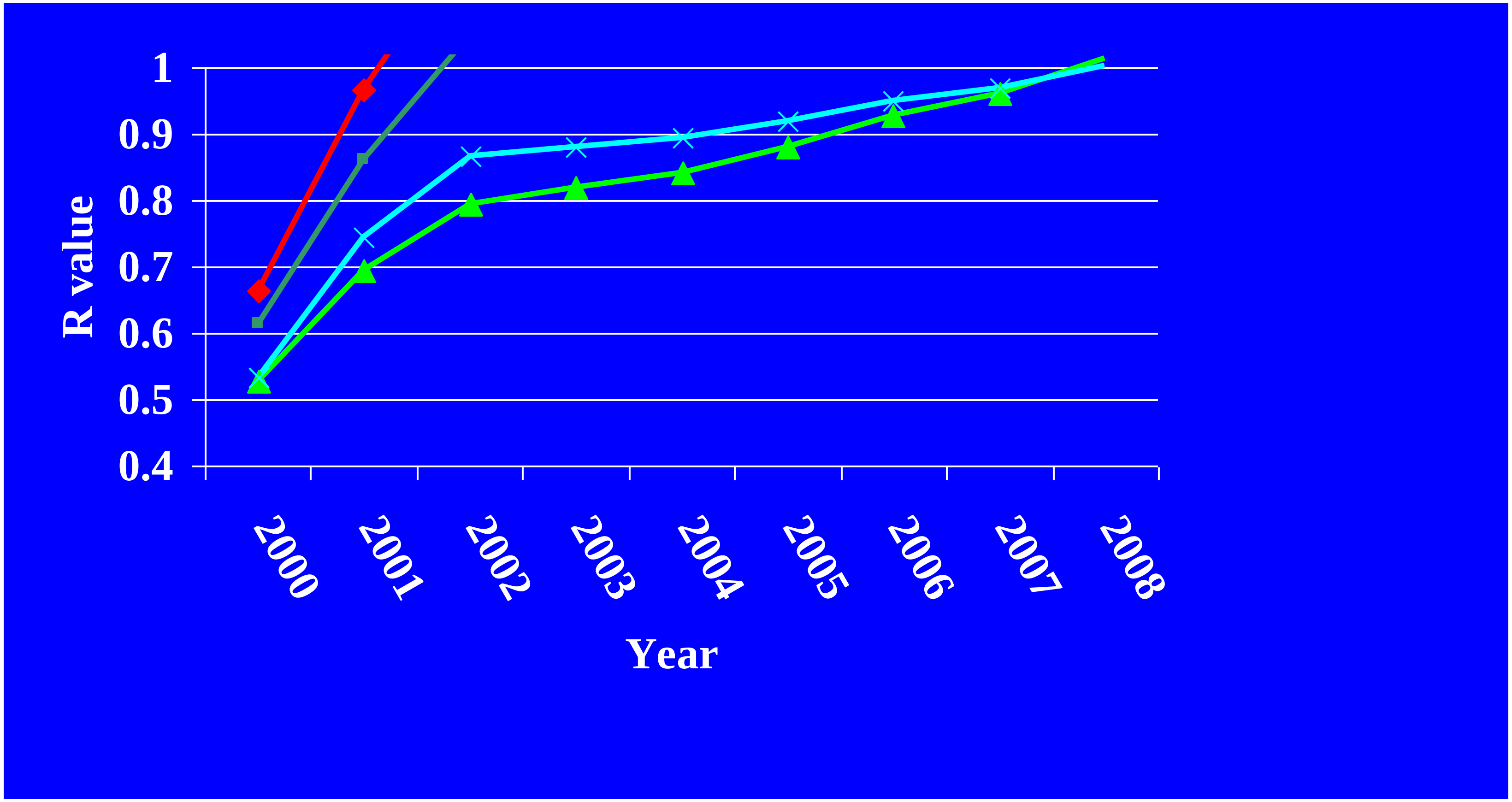
Impact of the 1998 measles control campaign in Australia



Effect of varying vaccination coverage at 5 years of age on R for measles



Projected R for selected Divisions of GP



Data source: ACIR

Measles, measles everywhere

- Ongoing measles epidemics
- Australia has declared measles elimination
- Modelling in 2014 to look at risk over next 20 years
- Shows increasing risks of large measles outbreaks over this period, in particular in the states of Queensland and New South Wales.
- In addition, there is wide variation in predicted R values by smaller geographic areas, although uncertainty in age-specific immunity limits the precision of our results.

Wood JG;Heywood AE;Menzies RI;McIntyre PB;MacIntyre CR, 2014, 'Predicting localised measles outbreak potential in Australia', Vaccine, http://dx.doi.org/10.1016/j.vaccine.2014.12.071

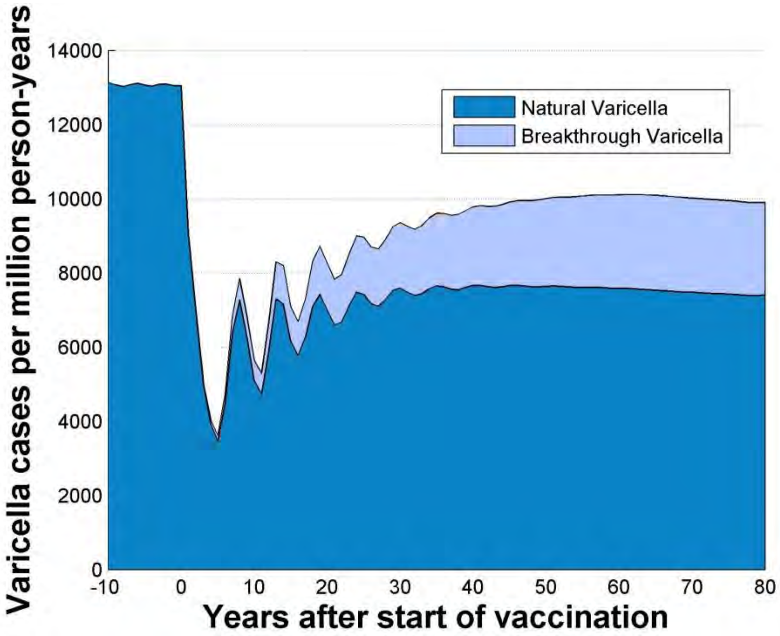
Policy dilemmas of VZV

- One or two dose?
- Effect of vaccine coverage
- Infant vaccination
- Elderly vaccination
- Boosting and HZ – Hope Simpson hypothesis

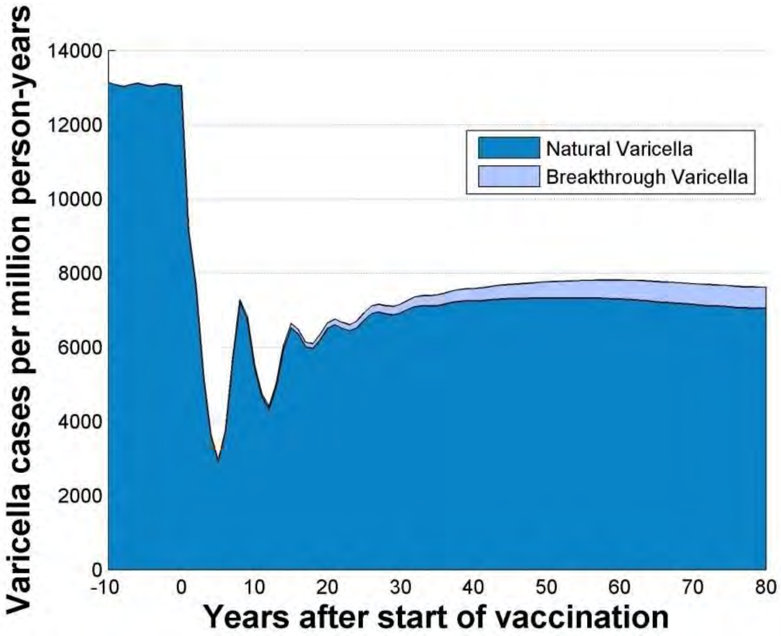
Varicella cases at low coverage (50%)

Both one-dose and two-dose strategies are expected to produce similar numbers of natural varicella. But the breakthrough varicella cases of one-dose strategy are more than three times of two-dose strategy.

One-dose strategy, 50% coverage



Two-dose strategy, 50% coverage

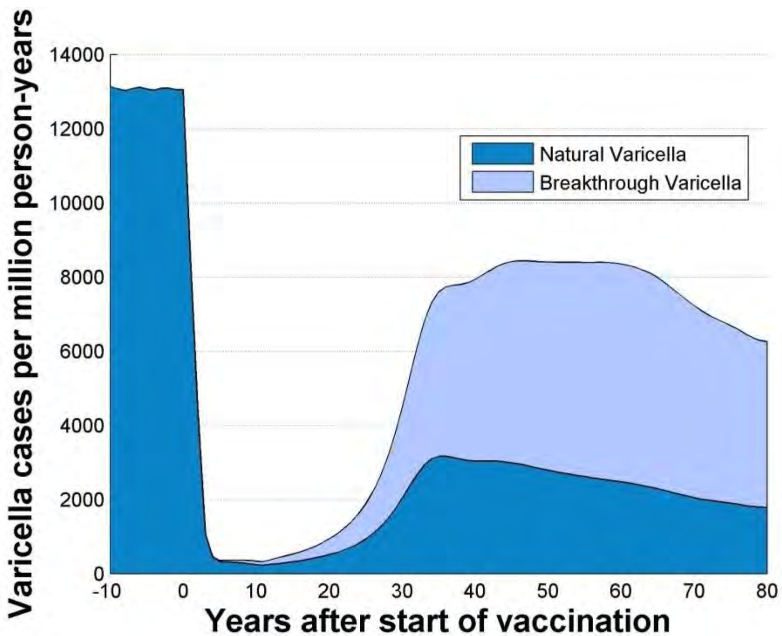


GAO Z;WOOD JG;GIDDING HF;NEWALL AT;MENZIES RI;WANG H;McINTYRE PB;MACINTYRE CR, 2015, 'Control of varicella in the post-vaccination era in Australia: a model-based assessment of catch-up and infant vaccination strategies for the future Epidemiology & Infection

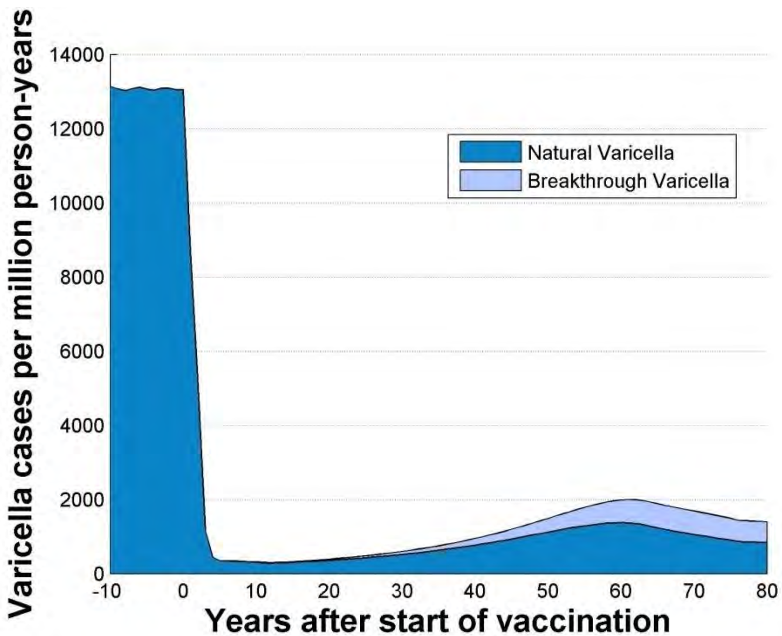
Varicella cases at high coverage (90%)

At equilibrium, VE (vaccine effectiveness) is 66% for one-dose strategy and 92% for two-dose strategy. A two-dose vaccination is expected to not only produce less natural varicella cases but also fewer varicella breakthrough cases. Breakthrough varicella cases in one-dose vaccinees are 7 times higher than two-dose vaccinees.

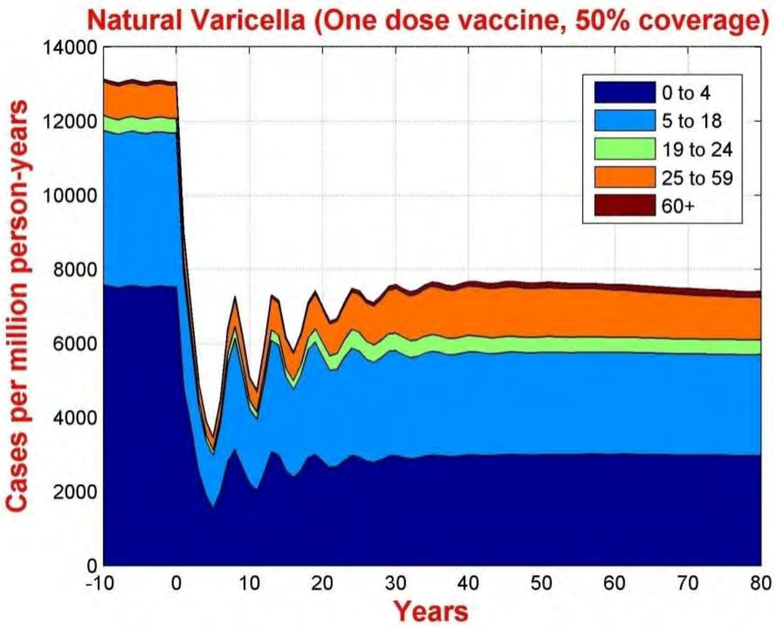
One-dose strategy, 90% coverage

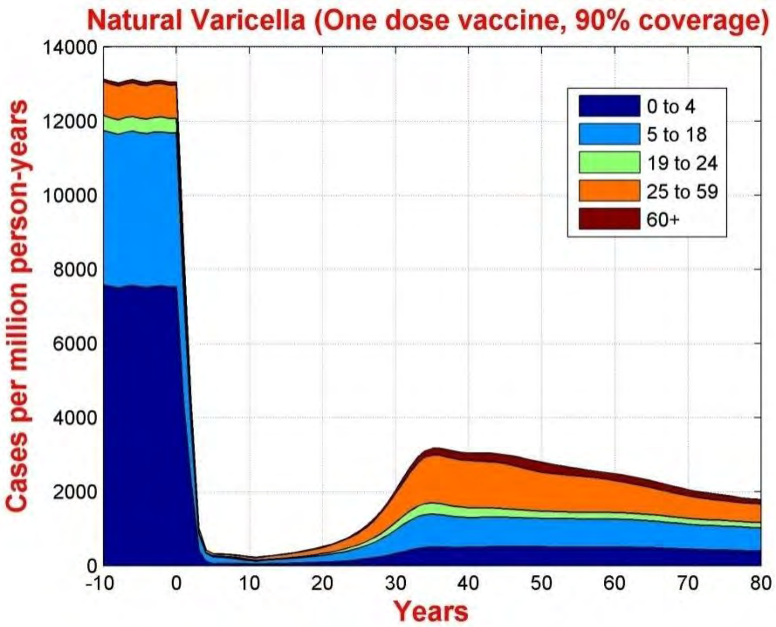


Two-dose strategy, 90% coverage



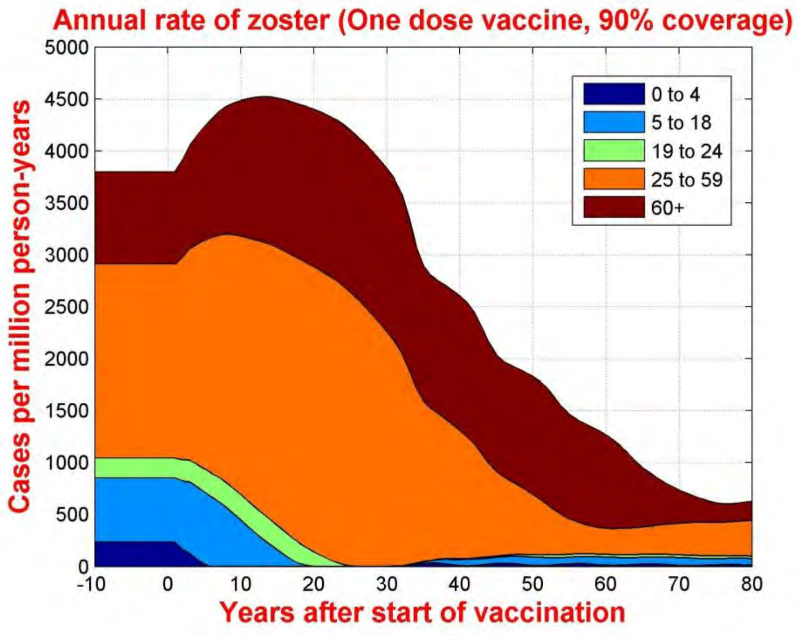
Age-specific natural varicella incidence for one-dose strategy



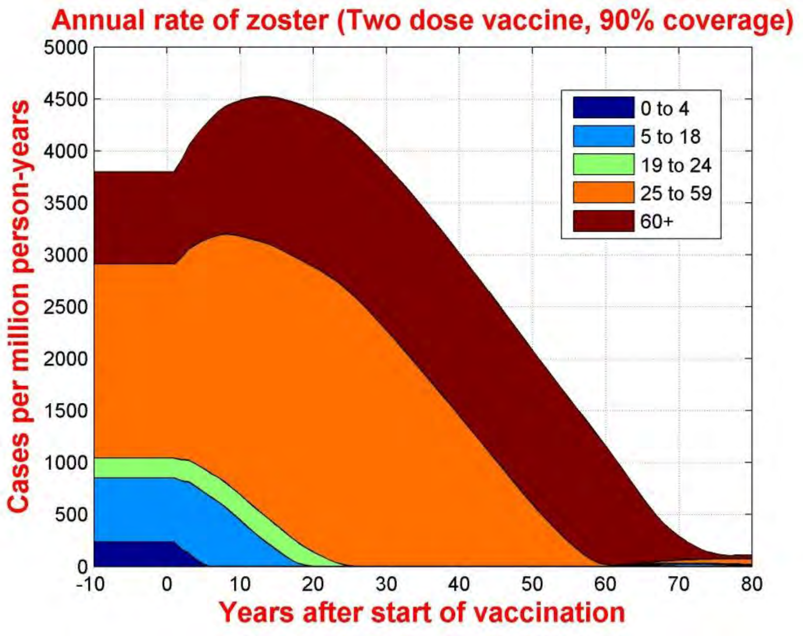


Age-specific zoster cases

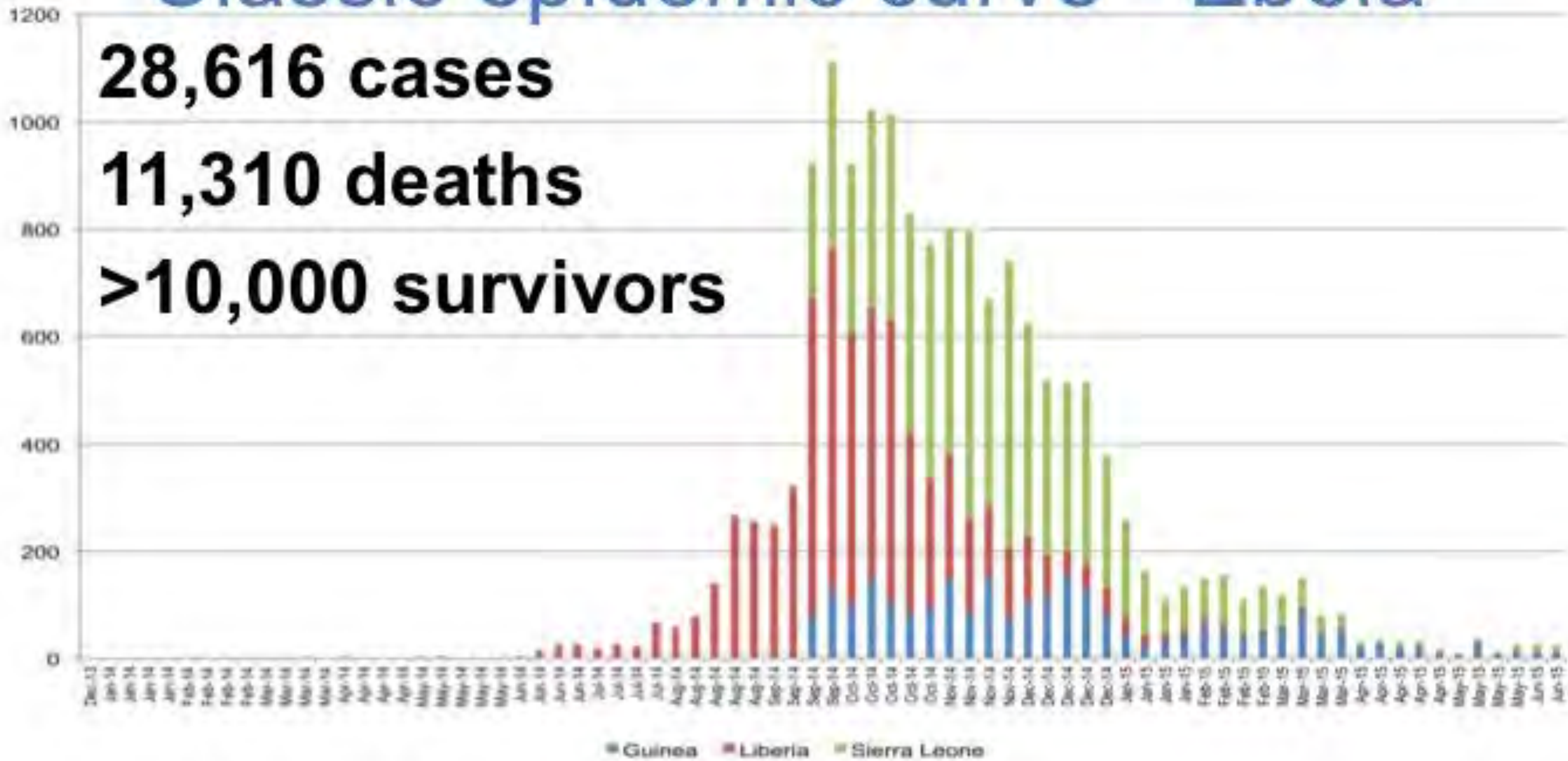
One-dose strategy



Two-dose strategy



Classic epidemic curve - Ebola



Data source: WHO

Modelling of public health action

- Ebola in West Africa
- No drugs or vaccines available
- Modelling of the epidemic showed lack of hospital beds to be a major problem
- Target: 70% of patients in ETUs to achieve control of the epidemic

Meltzer M et al.
https://www.cdc.gov/mmwr/preview/mmwrhtml/su6303a1.htm?s_cid=su6303a1_w

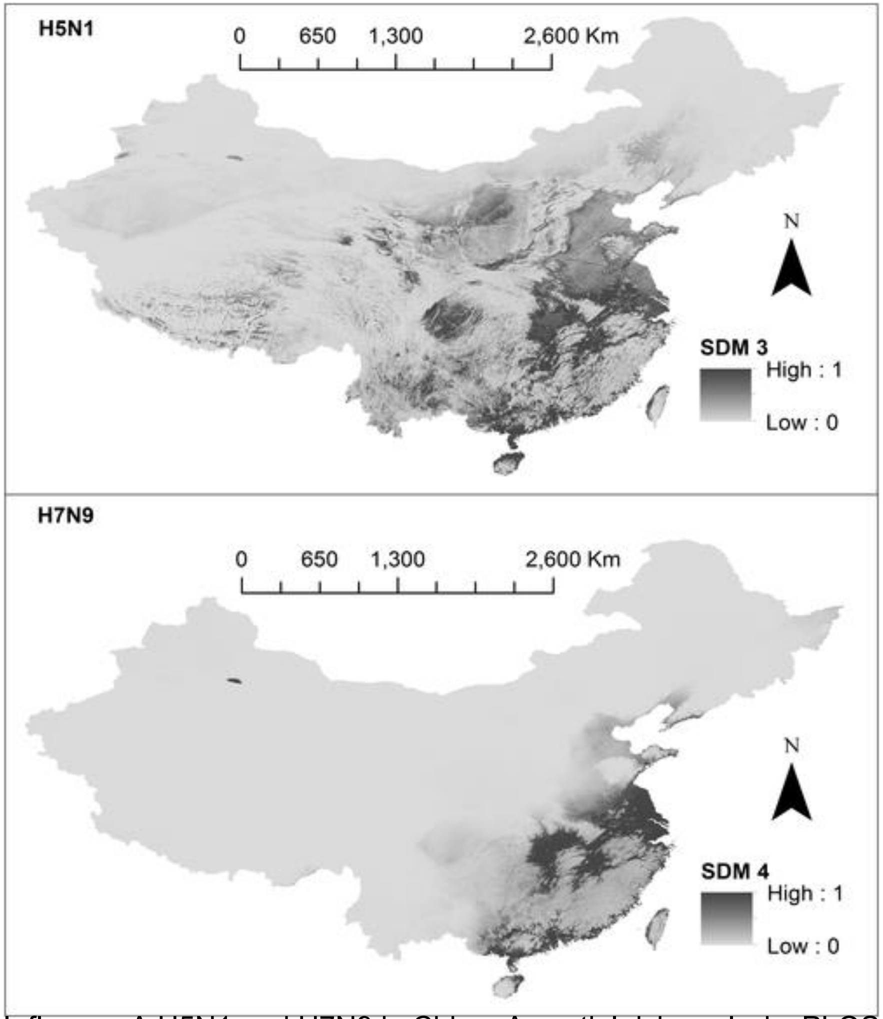
Transport network modelling and risk analysis

- MERS CoV – emerged in KSA, spread to 26 countries
- Largest epidemic outside of KSA in South Korea
- Cases linked to travel to Middle East
- Transport network modelling
- Identifies countries by level of risk of MERS importation
- Allows prioritising of country specific plans (eg hospital triage protocols)
- Highest risk country is India, has not yet had imported MERS.

Gardner, Chughtai, MacIntyre. Risk of global spread of MERS-Cov via the air transport network. J Trav Med. 2016; 20 (6).

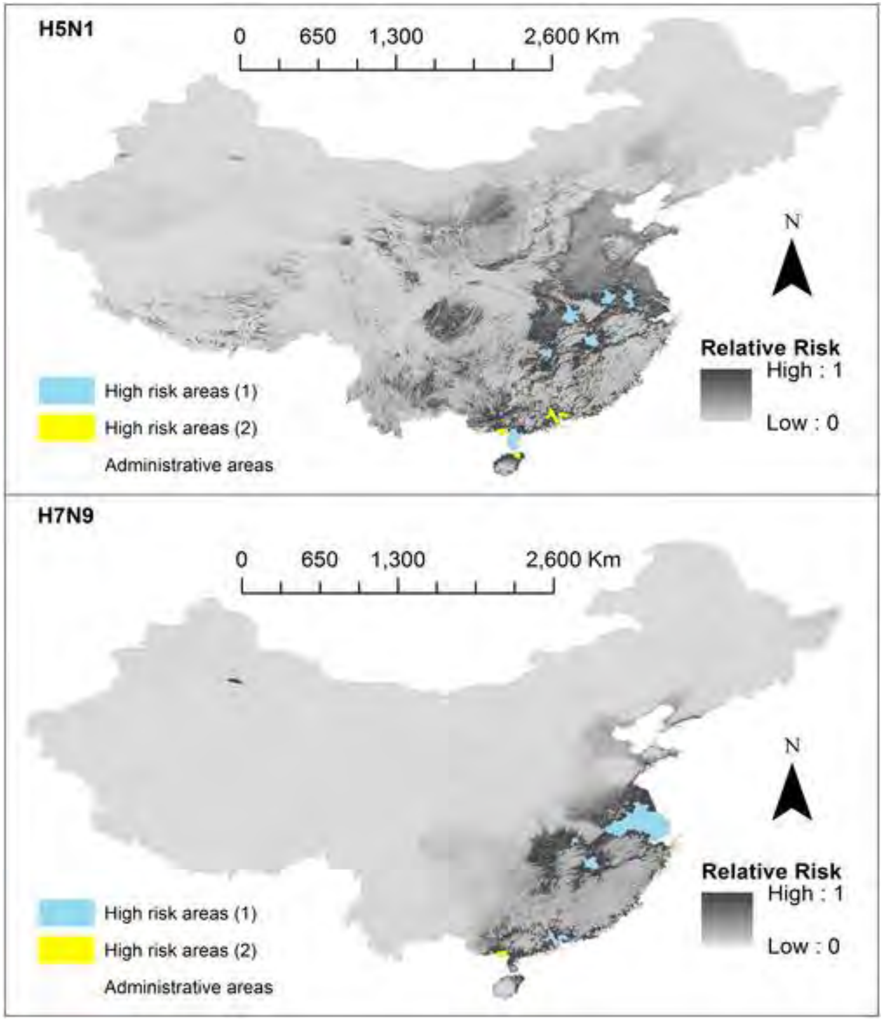
Fig 2. Species Distribution Models (SDMs) built using Maxent.

Geospatial modelling



Bui CM, Gardner L, MacIntyre R, Sarkar S (2017) Influenza A H5N1 and H7N9 in China: A spatial risk analysis. PLOS ONE 12(4): e0174980. https://doi.org/10.1371/journal.pone.0174980
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0174980

Fig 5. High risk areas.



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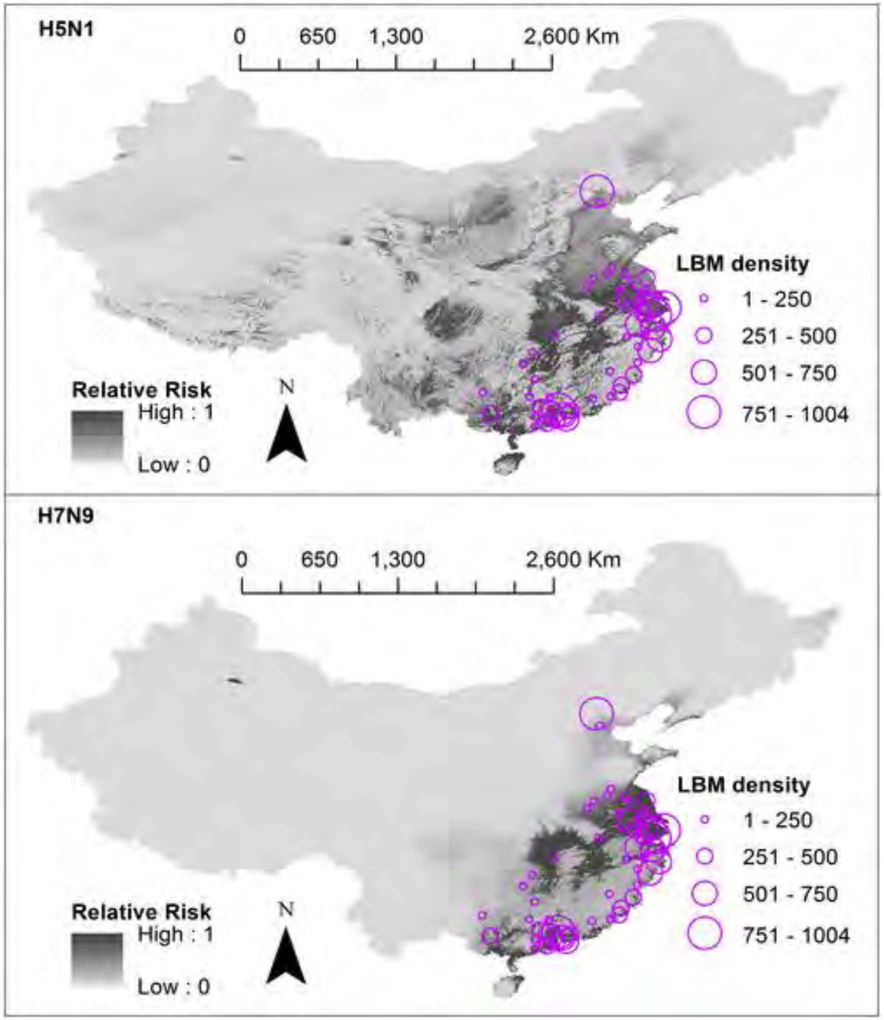
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0174980

Fig 6. Risk models overlayed with live bird market density.



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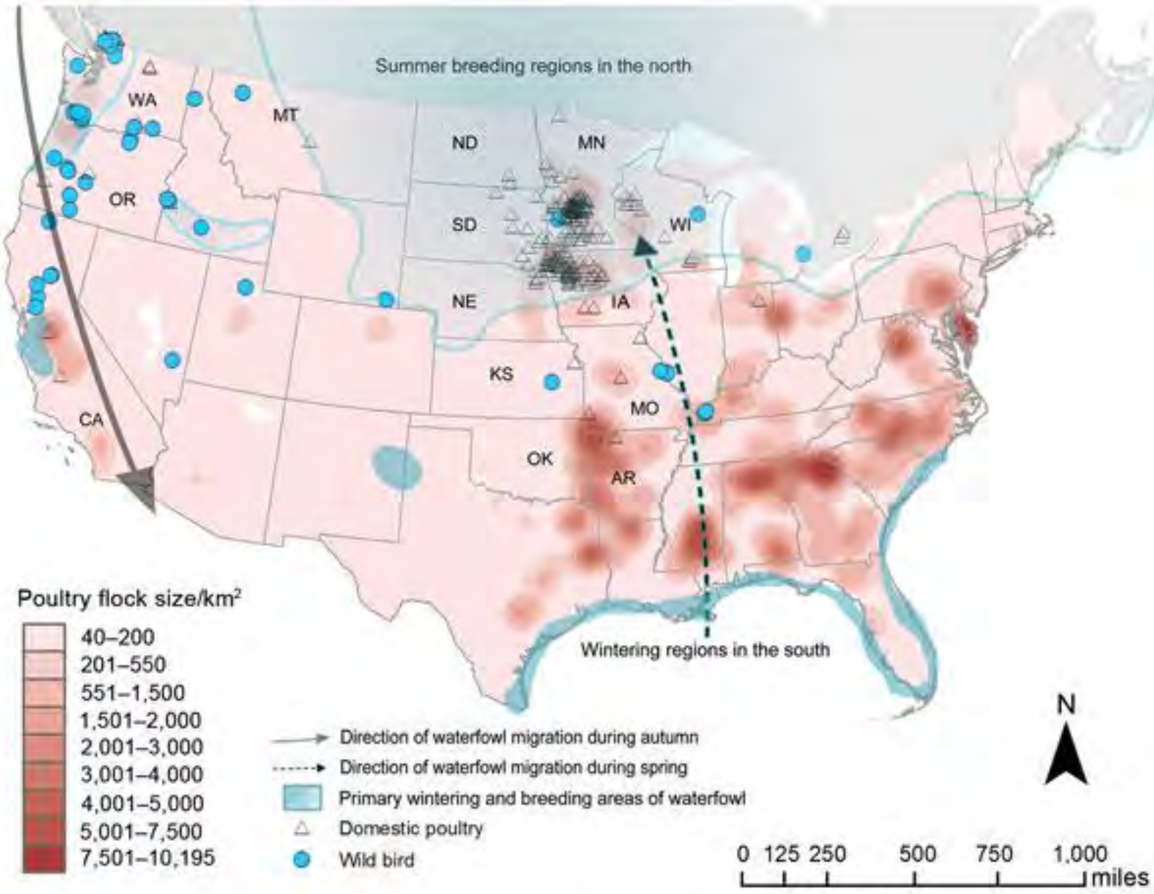

Highly Pathogenic Avian Influenza Virus, Midwestern United States

Chau M. Bui, Lauren M. Gardner, and C. Raina MacIntyre

Emerging Infectious Diseases. Volume 22, Number 1—January 2016

What do stakeholders want?

- We asked them - government, health, defense, general practice, labs
- Modeling underused in Australia and its potential is poorly understood by practitioners involved in epidemic responses.
- Ideal modeling tools for operational use would be easy to use, clearly indicate underlying parameterization and assumptions, and assist with policy and decision making.
- *“The most useful thing a model producesd is the 3 lines at the bottom that says this means that [or] when you do this, this, and this, this will happen or we think this will happen.”*

Muscatello DJ, Chughtai AA, Heywood A, Gardner LM, Heslop DJ, MacIntyre CR. Translation of real-time infectious disease modeling into routine public health practice. Emerg Infect Dis. 2017 May [date cited]. http://dx.doi.org/10.3201/eid2304.161720

Modelling as good science

- Many utilities, many methods
- Complex systems/agent based models not discussed
- Multidisciplinary
- Underpinned by good data and sound assumptions
- Transparent and easily reproducible
- Not “black box” models

Modelling

- useful in the design of VPD control and elimination strategies
- informing policy and funding decisions
- Risk analysis
- useful in anticipation of emergencies – ensures that rational planning and prioritisation.
- gives additional information to routine surveillance data, and allows forecasting

Thank you