Public Health England

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

The cost-effectiveness of extending the seasonal influenza immunisation programme to school-aged children: the exemplar of the decision in the United Kingdom

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Stopping the transmission of influenza and protecting the most vulnerable

Global Annual Incidence per 100,000 of severe influenza in children (meta analysis)

	Incidence (95%CI)
Developing countries	
<6 mo. old	**290(200 - 410)**
0-11 mo. old	280 (190 - 410)
0-59 mo. old	170 (110 - 250)
Industrialized countries	
<6 mo. old	**340 (230 - 500)**
0 – 11 mo. old	230 (180 - 300)
0 – 59 mo. old	120 (90 - 170)

Nair et al., Lancet 2011; 378: 1917–30

Current annual seasonal trivalent inactivated vaccine (TIV) programme in the UK

- All high risk groups under 65 years
- All 65+ year olds
- Problems :
  - efficacy of TIV in elderly and the very young is poor
  - most vulnerable groups are the elderly and the very young

And the situation in the UK

Table 4 Influenza-attributable GP consultations and hospitalisation rates by age, entire population and ratio of consultations to admissions (95% confidence intervals).

Age	GP consultations annual rate per 100,000 (±95% CI)			Hospitalisations annual rate per 100,000 (±95% CI)			Ratio GP consultations: hospital admissions (±95% CI)
	Flu A	Flu B	All Flu	Flu A	Flu B	All Flu	All Flu
<6 m	4829 (233)	2532 (195)	7361 (304)	192 (9)	138 (8)	330 (12)	22.3 (22.1–23.6)
6 m–4 y	3916 (137)	2174 (101)	6090 (170)	149 (4)	26 (3)	175 (5)	34.9 (33.5–36.3)
5 y–14 y	2131 (62)	1744 (88)	3875 (107)	12 (0.8)	2 (0.2)	14 (0.8)	270 (254–288)
15–44 y	1327 (25)	552 (24)	1878 (35)	12 (0.3)	0 (0)	12 (0.3)	160 (155–164)
45–64 y	1468 (26)	361 (21)	1829 (34)	22 (0.6)	5 (0.2)	27 (0.6)	68.1 (66.1–70.0)
65+ y	582 (26)	0 (0)	582 (26)	63 (3)	0 (0)	63 (3)	9.2 (8.6–9.8)
All Ages	1496 (17)	660 (16)	2156 (23)	31 (0.6)	4 (0.2)	34 (0.6)	62.9 (61.6–64.2)

Cromer D, et al., J Infect (2013)

What to do? the British philosophy

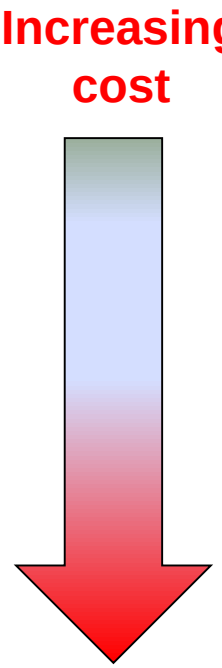
- Public health philosophy based on utilitarianism
- A government should use public resources to maximize the well being of the society
- Problem: how to quantify the “well being” when dealing with a public health intervention?

Quantifying the public health impact of an intervention

- Need a measurement which takes into account
    1. The change in years of life
    2. The change in term of quality of life (e.g. lost of mobility, pain…)
- The notion of Quality Adjusted Life Years (QALY) has been chosen as a measure in the UK
- One year of perfect health is equal to one QALY while death is 0 QALY
- Impact of intervention assessed using ICER measured in £/QALY
- 20000£/QALY threshold for cost-effective interventions

Extensions to current programme

- Extend to low-risk:
  - 2-4 years
  - 50-64 years
  - 5-16 years
  - 2-4 & 50-64 years
  - 2-16 years
  - 2-16 & 50-64 years
  - 2-64 years
- Coverage assumed to be 50% in low-risk groups



Net additional cost
£ 14m

£282m

Schematic of approach

Epidemic parameters
- Reproduction number
- Incubation period
- Infectious period
- Susceptibility profile
- Mixing patterns
- ……

Data
- RCGP
- Swabbing
- Serology

Vaccine assumptions
- Coverage
- By age & risk
- By year & strain
- Efficacy

Epidemic projections

Outcomes
- Risk and age:
  - CFR
  - Hospit.
  - QALY loss
  - …

Costs
- Hospitalisation
- Vaccine
- Delivery
- …

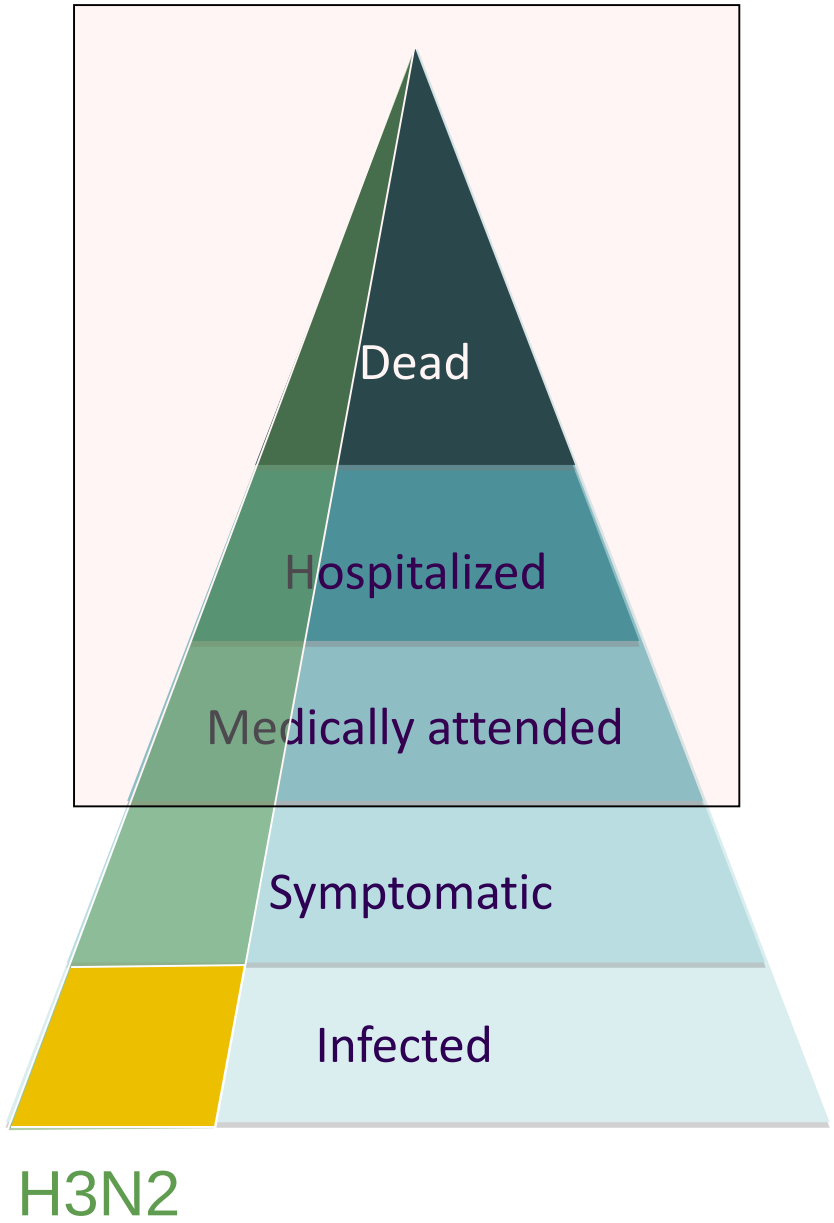
Projections in relevant units, & CEA

Mathematical models of infectious diseases

- Compartmental models
- Based on the SEIR structure
- Include age structure and risk groups
- “Easy” to produce a model, difficult to fit to surveillance data in the case of influenza

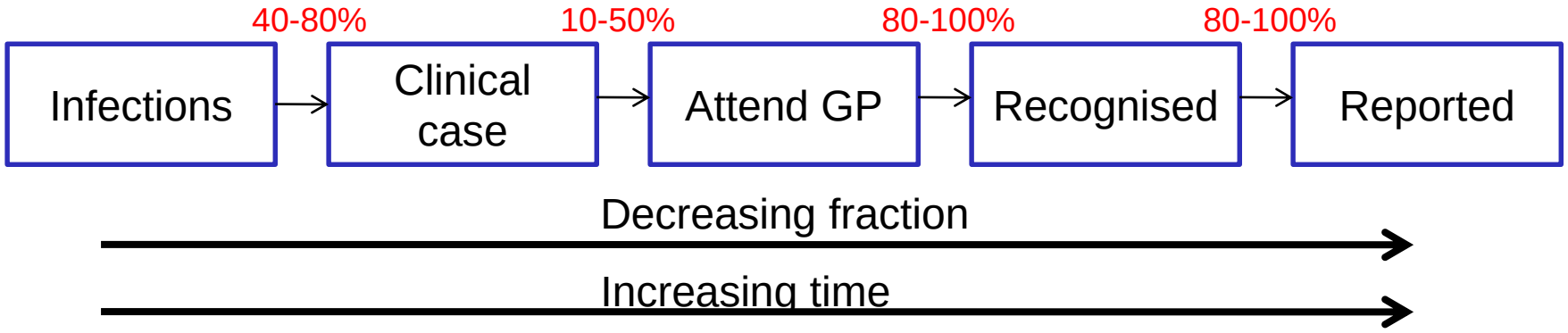
Severity pyramid ►ILI ► different possible pathogens

Only the top is observed by surveillance



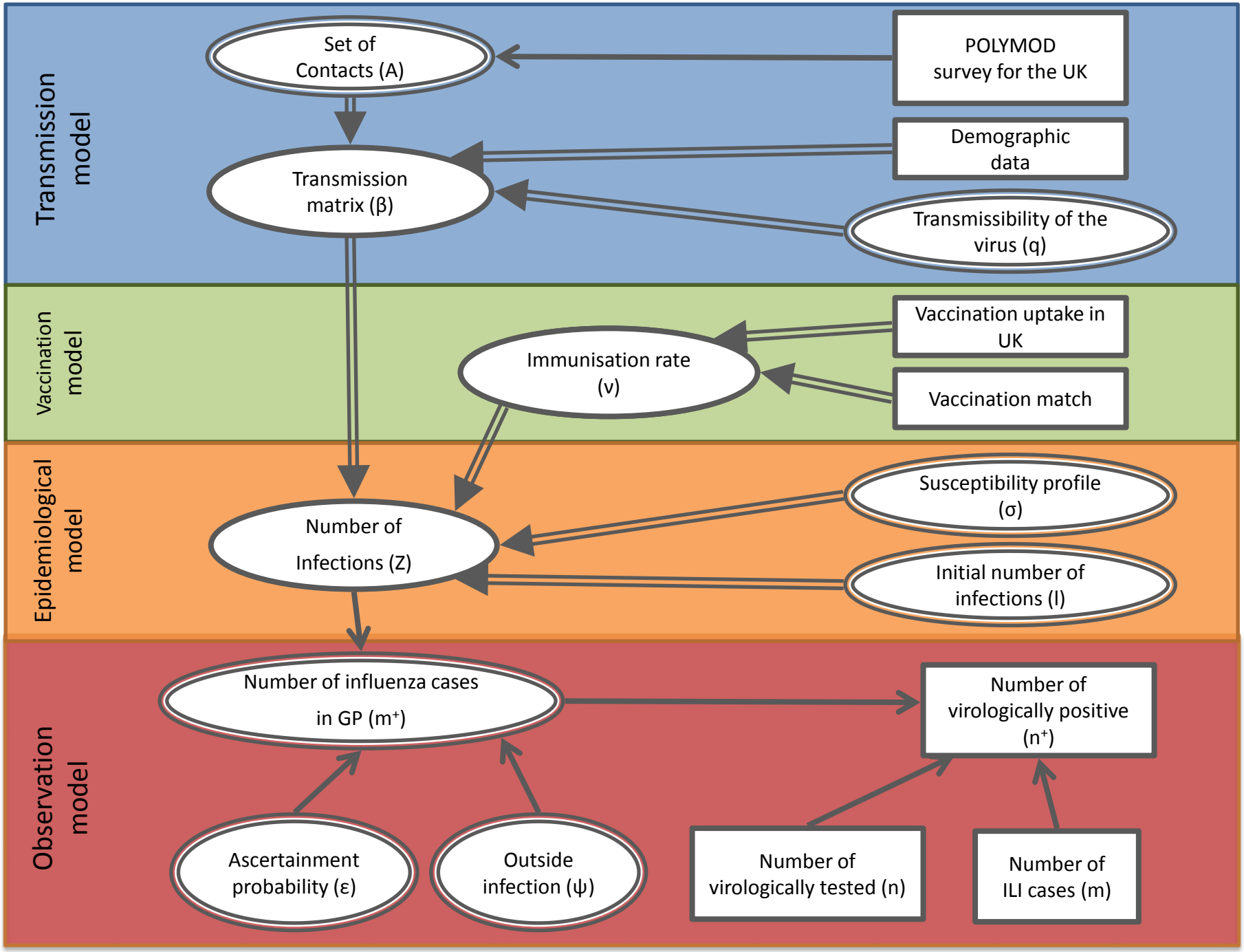
The problem of scale: nowcasting & forecasting using aggregate data

- Need to track depletion of susceptibles (i.e. infections)
- The data (i.e. # cases, or GP consultations, or deaths) gives us just a fraction of the infections
- What fraction?
  - i.e. what fraction of infections are reported?



Complex mathematical and statistical problem

- Evidence synthesis where mathematical modelling is used to linked different data sources
- Breaks down into elementary processes
- Bayesian approach to estimate uncertainty
- Dynamical transmission model and probabilistic observation model


Transmission model
Set of Contacts (A)
POLYMOD survey for the UK
Demographic data
Transmission matrix (β)
Transmissibility of the virus (q)
Vaccination model
Vaccination uptake in UK
Immunisation rate (ν)
Vaccination match
Epidemiological model
Susceptibility profile (σ)
Number of Infections (Z)
Initial number of infections (I)
Observation model
Number of influenza cases in GP (m+)
Number of virologically positive (n+)
Ascertainment probability (ε)
Outside infection (ψ)
Number of virologically tested (n)
Number of ILI cases (m)

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PLOS | MEDICINE

Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study

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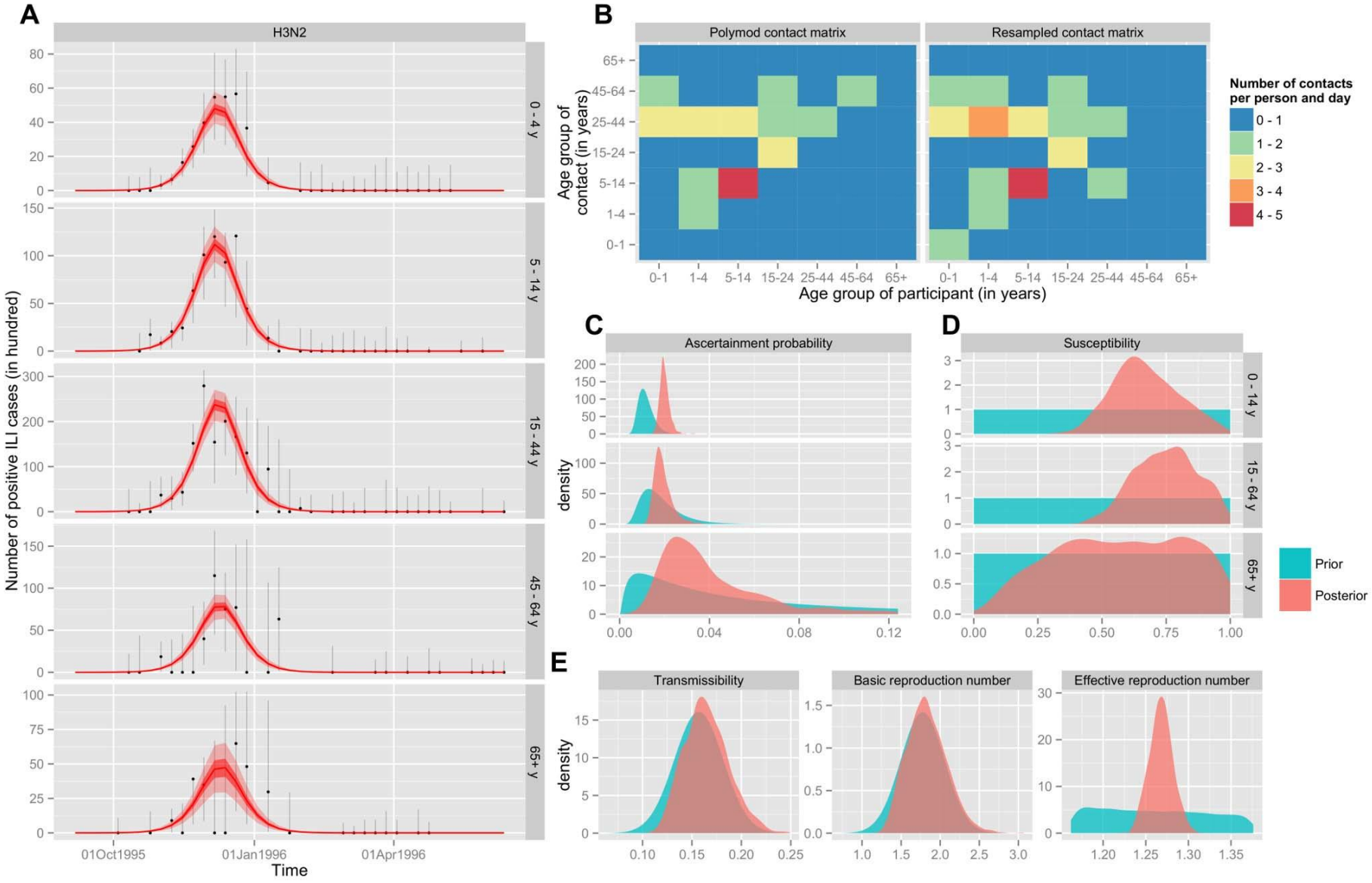
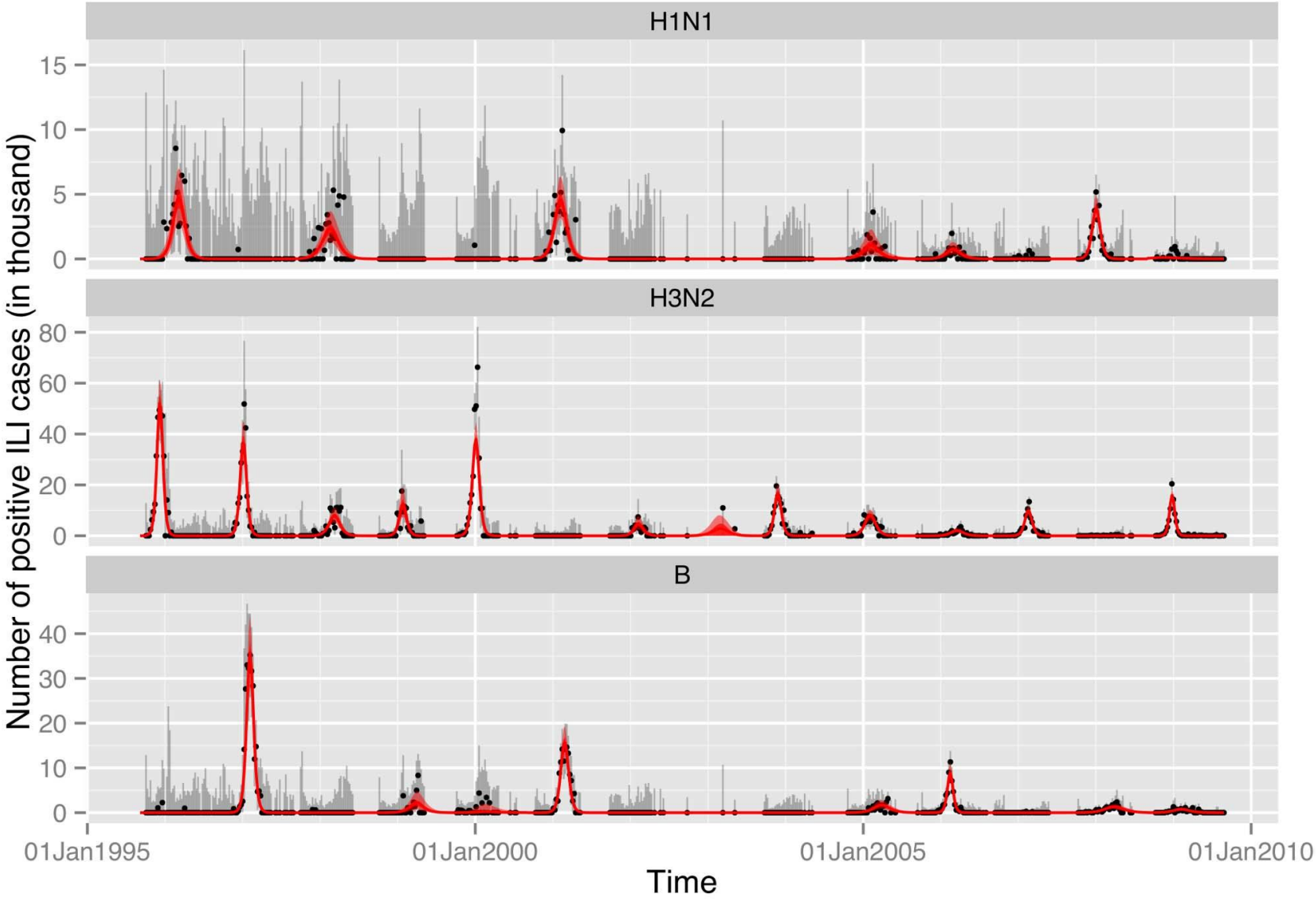
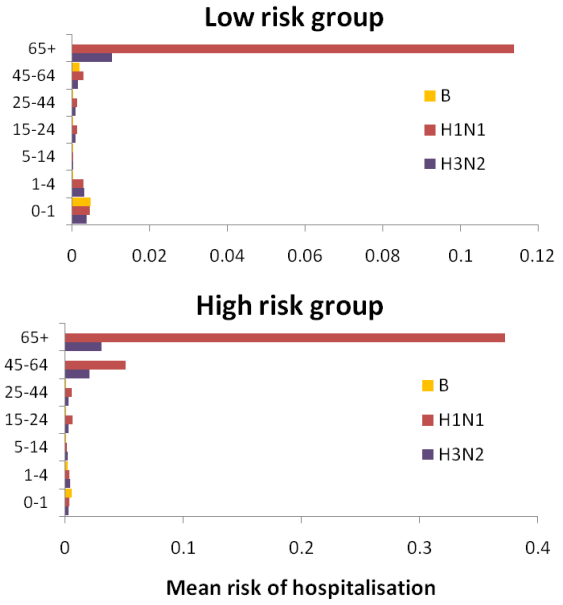

A
H3N2
0 - 4 y
5 - 14 y
15 - 44 y
45 - 64 y
65+ y
Number of positive ILI cases (in hundred)
01Oct1995
01Jan1996
01Apr1996
Time
B
Polymod contact matrix
Resampled contact matrix
Age group of contact (in years)
65+
45-64
25-44
15-24
5-14
1-4
0-1
Age group of participant (in years)
Number of contacts per person and day
0 - 1
1 - 2
2 - 3
3 - 4
4 - 5
C
Ascertainment probability
density
D
Susceptibility
0 - 14 y
15 - 64 y
65+ y
Prior
Posterior
E
Transmissibility
Basic reproduction number
Effective reproduction number
density


H1N1
H3N2
B
Number of positive ILI cases (in thousand)
15
10
5
0
80
60
40
20
0
40
30
20
10
0
01Jan1995
01Jan2000
01Jan2005
01Jan2010
Time

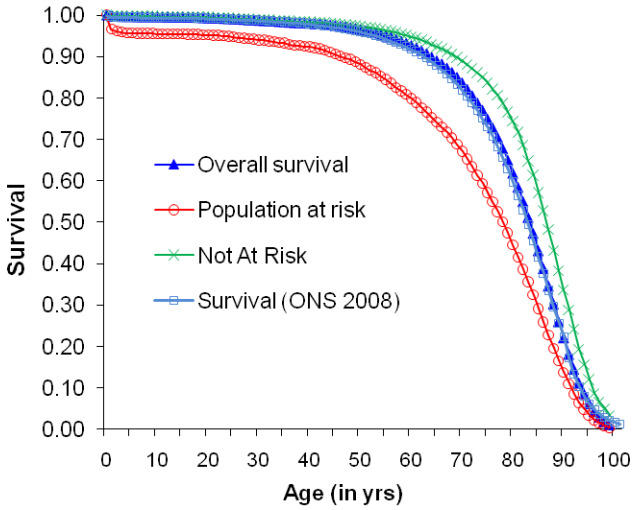
Linking infection risks with disease risks

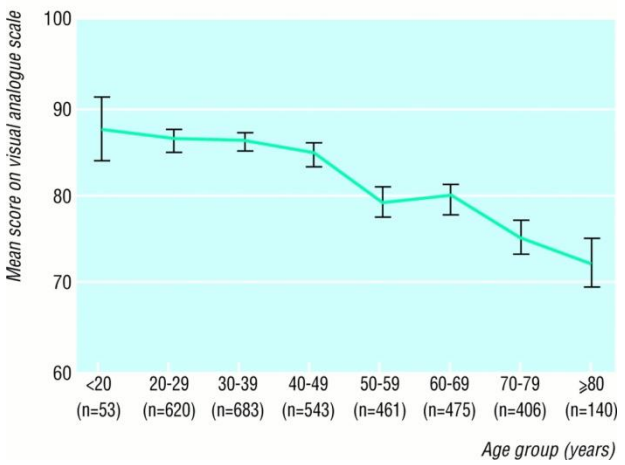
- Annual cases of infection by strain & age group
- Annual number of outcomes (e.g. hospit)
- Derive risk ratios
- Problems:
  - Age groups not always identical assume outcomes distributed by pop size
  - Some years very low (zero) infections estimated
  - Labbase (burden) does not distinguish H1 and H3
  - Derived risk ratios from years when relatively large number of cases (and mostly 1 strain of flu A)
    - A H1N1: 2000/1 and 2007/8
    - A H3N2: 2003/4, 2004/5 and 2006/7
    - B: 2000/1 and 2005/6



Costs & QALYs

- Costs of vaccination from DH
- NHS reference costs for treatment
- Non-fatal QALYs lost from literature
- Fatal cases assumed to lose average risk and age-specific life-expectancy adjusted for average age-specific QoL (from RCGP)

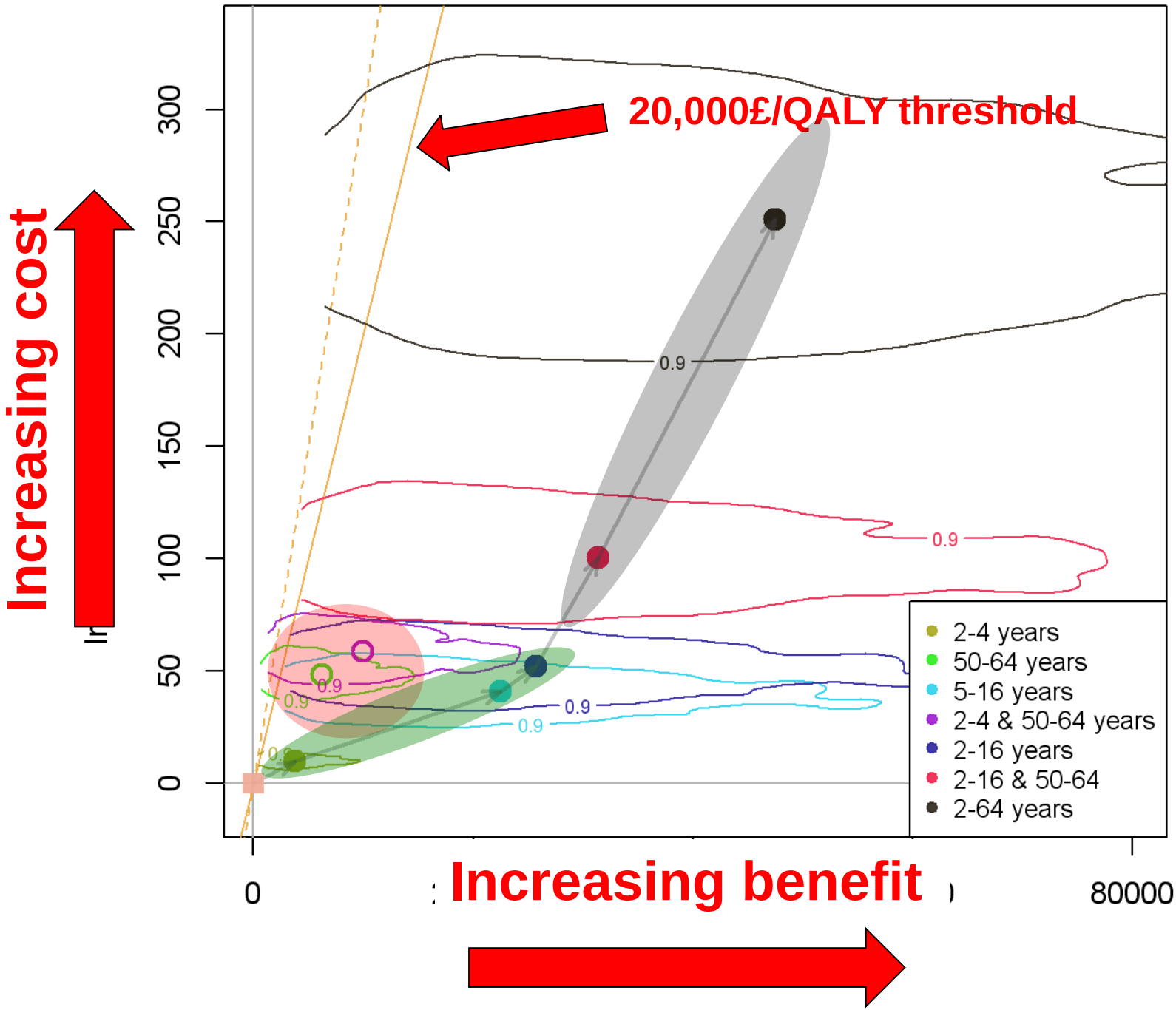




Kind P et al. BMJ 1998;316:736-741

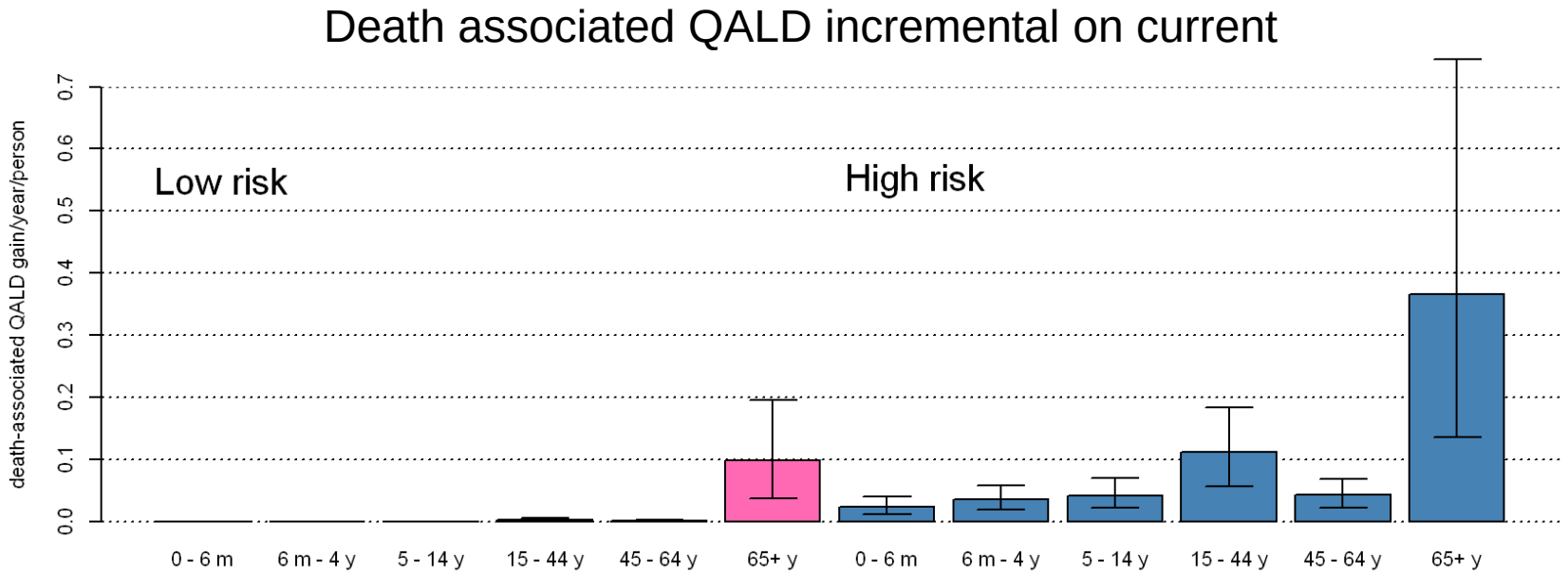
Incremental cost-effectiveness

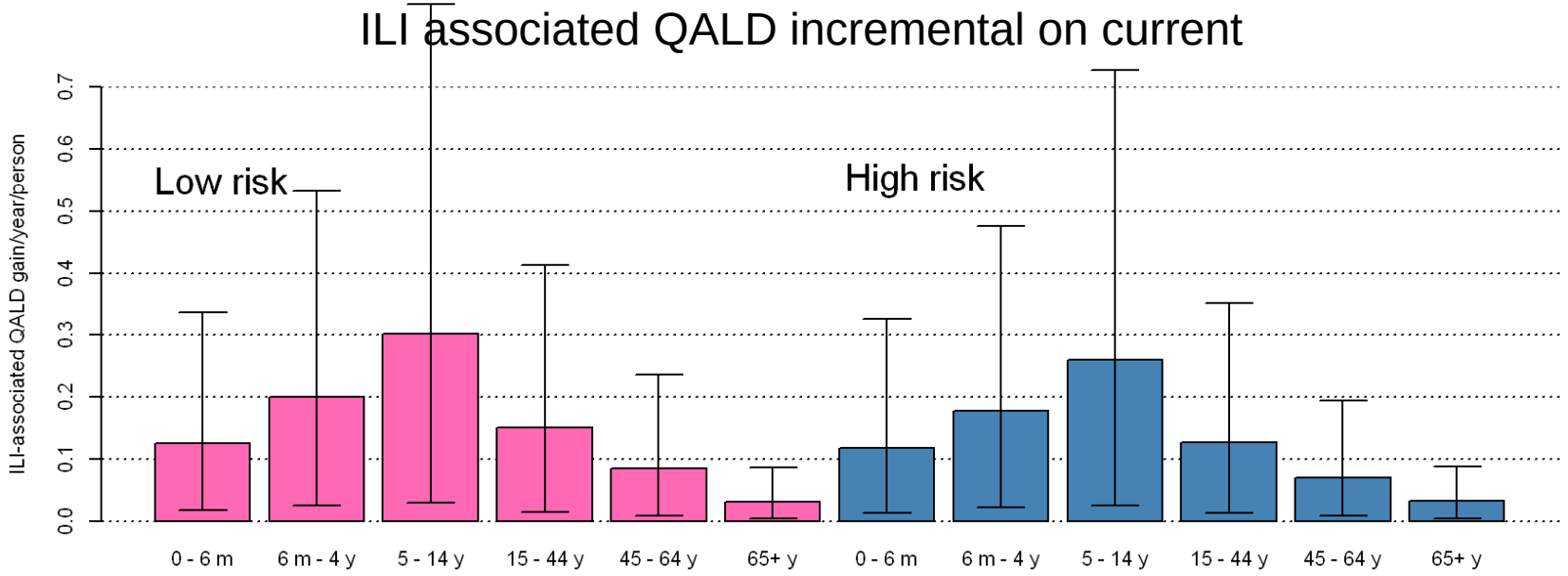
- Rank scenarios by increasing cost
  - 2-4 years
  - 50-64 years
  - 5-16 years
  - 2-4 & 50-64 years
  - 2-4 & 5-16 years
  - 2-4 & 5-16 & 50-64 years
  - 2-64 years
- Remove the ‘dominated’ ones (more money, less QALYs saved
- Compute incremental CEAC (cost-effectiveness acceptability curve)
- Stop until not CE anymore


Increasing cost
20,000£/QALY threshold
0
50
100
150
200
250
300
0.9
0.9
0.9
0.9
0.9
0.9
2-4 years
50-64 years
5-16 years
2-4 & 50-64 years
2-16 years
2-16 & 50-64
2-64 years
0
80000
Increasing benefit

Are we vaccinating the kids to protect their grandparents?

- Ethical issue with recommending a treatment for the benefit of others


Death associated QALD incremental on current
death-associated QALD gain/year/person
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Low risk
High risk
0 - 6 m
6 m - 4 y
5 - 14 y
15 - 44 y
45 - 64 y
65+ y
0 - 6 m
6 m - 4 y
5 - 14 y
15 - 44 y
45 - 64 y
65+ y


ILI associated QALD incremental on current
ILI-associated QALD gain/year/person
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Low risk
High risk
0 - 6 m
6 m - 4 y
5 - 14 y
15 - 44 y
45 - 64 y
65+ y
0 - 6 m
6 m - 4 y
5 - 14 y
15 - 44 y
45 - 64 y
65+ y

Cost-effectiveness of vaccinating children

- Cost-effective to vaccinate school children for their own benefit (i.e. ignoring benefits to other groups)
  - ICER=8155 £/QALY
  - Mean Net Benefit £107m [90%CI: -£34m £390m]
  - Burden exclusively in term of saved influenza episodes and hospitalisations

And finally the decision!

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Flu vaccines for all children

COMMENTS (511)

All two to 17-year-olds in the UK are to be offered annual flu vaccinations.

If 30% take up the offer, there will be 11,000 fewer hospitalisations and 2,000 fewer deaths each year, the chief medical officer for England says.

The children will be immunised using a nasal spray rather than an injection, starting in 2014 at the earliest.

Nasally introduced flu vaccine

The future

- The implementation of the programme has started in 6 pilot areas this season for the 4-11, and nationally for the 2-3
- It will be extended next year to more age groups

Main improvements / weaknesses

- Fitting:
  - Serology
  - Serial fitting
  - (more swabbing data)
- Burden
  - Deaths & life-expectancy (vaccinate everyone?)
  - Linking infection & burden (different data sources)
- Low activity era: will this continue?
- Transmission
  - Model suggests that children play a key role
  - Cluster randomised trials (e.g. Loeb et al.) support this, but others have argued against

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- Douglas Flemming (Royal College of Practitioner)
- Tom Barlow, Peter Grove (UK Department of Health)

Increment	ICER (£/QALY)	% < £20,000/QALY	% < £30,000/QALY	Net benefit in £M	95% credibility interval
Current → 2-4y	2647	100	100	71.4	(10.4, 247.0)
2-4y → 5-16y	1611	100	100	372.8	(79.4, 1242.9)
5-16y → 2-16y	3494	100	100	55.7	(7.2, 208.2)
y → 2-16y & 50-64y	8458	86	95	75.2	(-14.9, 327.9)
y & 50-64y → 2-64y	9330	81	93	188.7	(-64.4, 919.9)