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Translating Outcomes from a Dynamic Transmission Model for Vaccination to Cost-Effectiveness Estimates: The Impact of Different Analytic Approaches on the Results

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Overview of Presentation

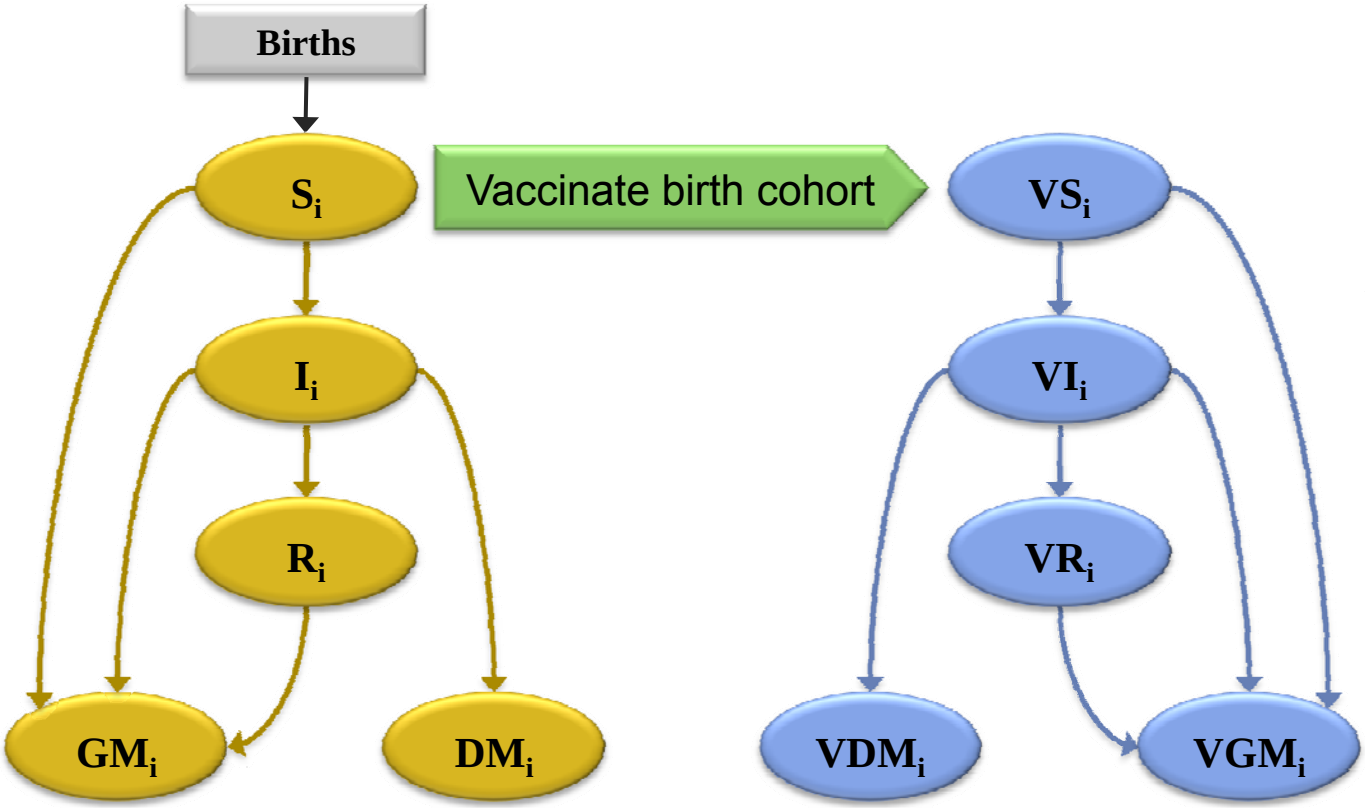
- Study Objectives
- Model Structure
  - SIR Model
  - Cost-Effectiveness Analyses
- Model Inputs
- Results
  - SIR Model Results
  - Cost-Effectiveness Results
- Conclusions
- Implications for Economic Evaluations of Vaccines

Study Objectives

- To compare the results of different methods that have been used to estimate the cost-effectiveness of vaccination programs using dynamic transmission models.

Model Structure – SIR Model

- A dynamic transmission model was programmed for varicella disease in England & Wales split into 3 compartments: susceptible, infectious, recovered (SIR).
- In each time step (e.g., 1 day), difference equations are used to transition people between compartments.



S = susceptible
I = infectious
R = recovered
V = vaccinated
GM = general-mortality death
DM = disease-related death
i denotes age group i (1 thru 8)

Model Structure – Cost-Effectiveness Analyses

- Cost & health outcomes for Vaccine Program and No Vaccine Program were calculated in 3 different ways:
  - **Cumulative Population Analysis:**
    Outcomes were summed across the entire population (vaccinated & unvaccinated, for all ages) cumulatively over a selected time horizon
  - **Steady-State Year Population Analysis:**
    Outcomes were summed across the entire population (vaccinated & unvaccinated, for all ages) for the steady-state year
  - **Lifetime Cohort Analysis:**
    Outcomes were summed for 1 birth cohort (vaccinated & unvaccinated) cumulatively over lifetime
- Cost-effectiveness estimates (e.g., incremental £/QALY gained) were then calculated for each analytic approach.
- For all 3 analyses, outcomes were discounted at 3.5% per year back to the start of the vaccination program.

Model Inputs

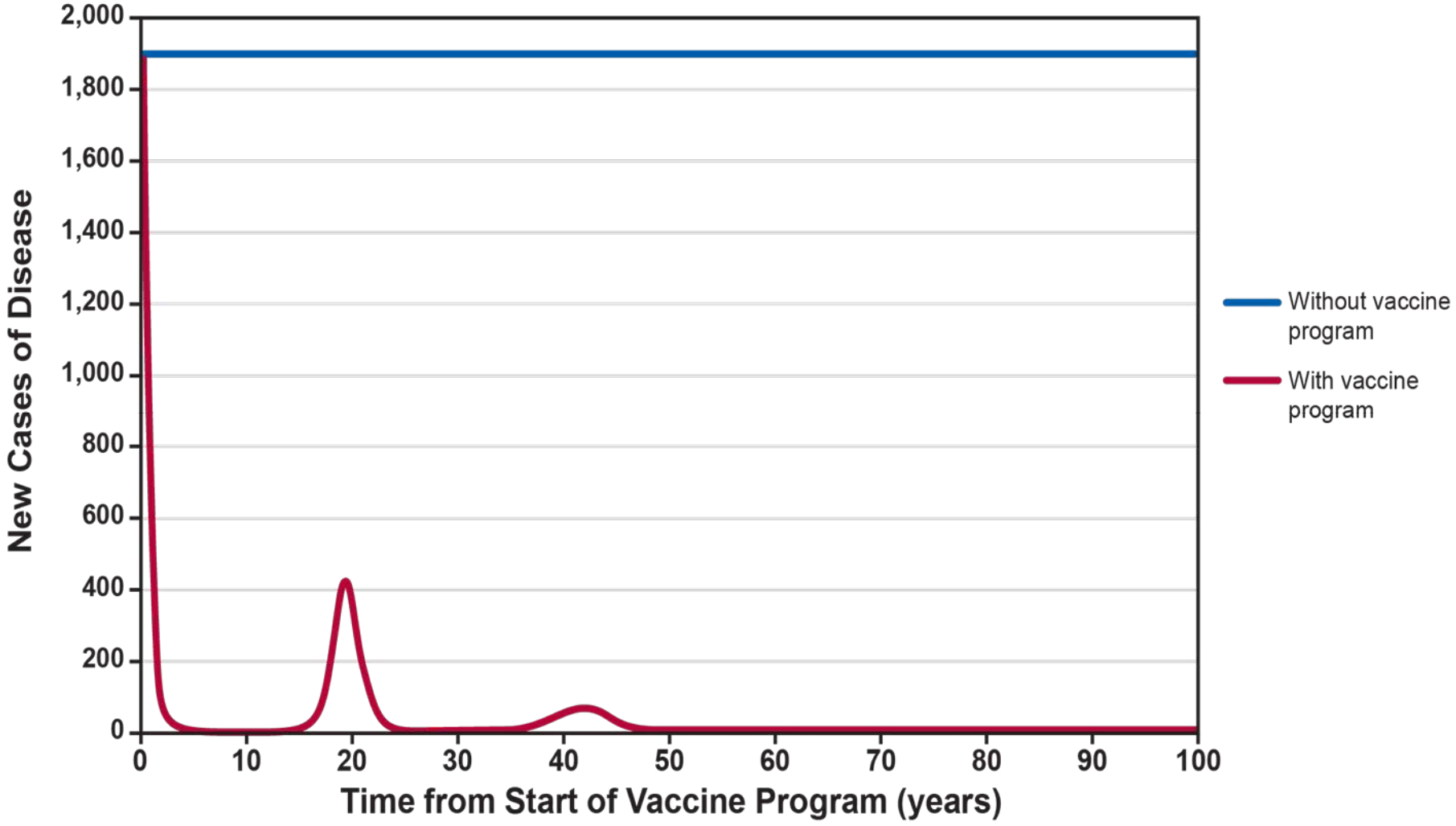
Parameter	Value	Reference	Sensitivity Range
Time Horizon	100 years	Assumption	1 year to 100 years
Discount Rate	3.5%	NICE, 2004	0%, 5%
Model Time Step	1 day	Vynnykky & White, 2010	0.1 day, 0.01 day
Duration of Disease	14 days	Brisson & Edmunds, 2000	Not varied
Vaccine Coverage	90%	Assumption	0% to 95%
Vaccine Efficacy	96%	Brisson & Edmunds, 2000	50% to 100%
Population Size, Annual Births, Annual All-Cause Mortality	Data by age*	Office of National Statistics, 2009	Not varied
Initial Force of Infection (λ_0)	Data by age*	Brisson & Edmunds, 2001	Not varied
Contact (WAIFW) Matrix	Assortative matrix	Brisson & Edmunds, 2000	Not varied
QALYs Lost per Case of Disease, Case Fatality Ratio	Data by age*	Brisson & Edmunds, 2003	- / + 50%
Cost per Case of Disease	Data by age* (£18.93 – £74.92)	Calculated from Brisson & Edmunds, 2003; inflated to 2010 £	-50%, +10x base case
Vaccine Cost per Course	£39.44	Brisson & Edmunds, 2003; inflated to 2010 £	£15, £200†

WAIFW = Who Acquires Infection From Whom

* Data for England & Wales for the following 8 age groups: <1, 1-4, 5-11, 12-19, 20-24, 25-44, 45-64, and 65+ years.

† Upper bound vaccine cost is similar to more expensive vaccines such as Gardasil, Cervarix, Prevenar-13 (BNF, 2012).

SIR Model Results: Cases of Disease Over Time With and Without Vaccine Program in England & Wales



Cost-Effectiveness Results: Results by Analysis Type

	Cumulative Population Analysis n = 54.8 million/year		Steady-State Year Population Analysis n = 54.8 million		Lifetime Cohort Analysis n = 699,000	
Parameter	**No Vaccine**	**Vaccine**	**No Vaccine**	**Vaccine**	**No Vaccine**	**Vaccine**
Costs*	£425,534,000	£722,601,000	£491,984	£807,165	£11,810,500	£24,567,300
QALYs*	1,606,180,000	1,606,280,000	1,856,380	1,856,530	17,653,100	17,655,700
ICER†	--	£3,141 (-36%)^	--	£2,165 (-56%)^	--	£4,904

Highest ICER

ICER = incremental cost-effectiveness ratio (incremental cost per QALY gained).
* All outcomes are for a 100 year time horizon discounted at 3.5% per year back to the start of the vaccine program. Costs are in 2010 pounds.
† All ICERs reflect that the vaccine program costs more and leads to more QALYs compared with no vaccine program.
^ Relative difference compared with the lifetime cohort analysis.

One-Way Sensitivity: Difference in ICERs Across Analysis Types for Extreme Values for 4 Parameters

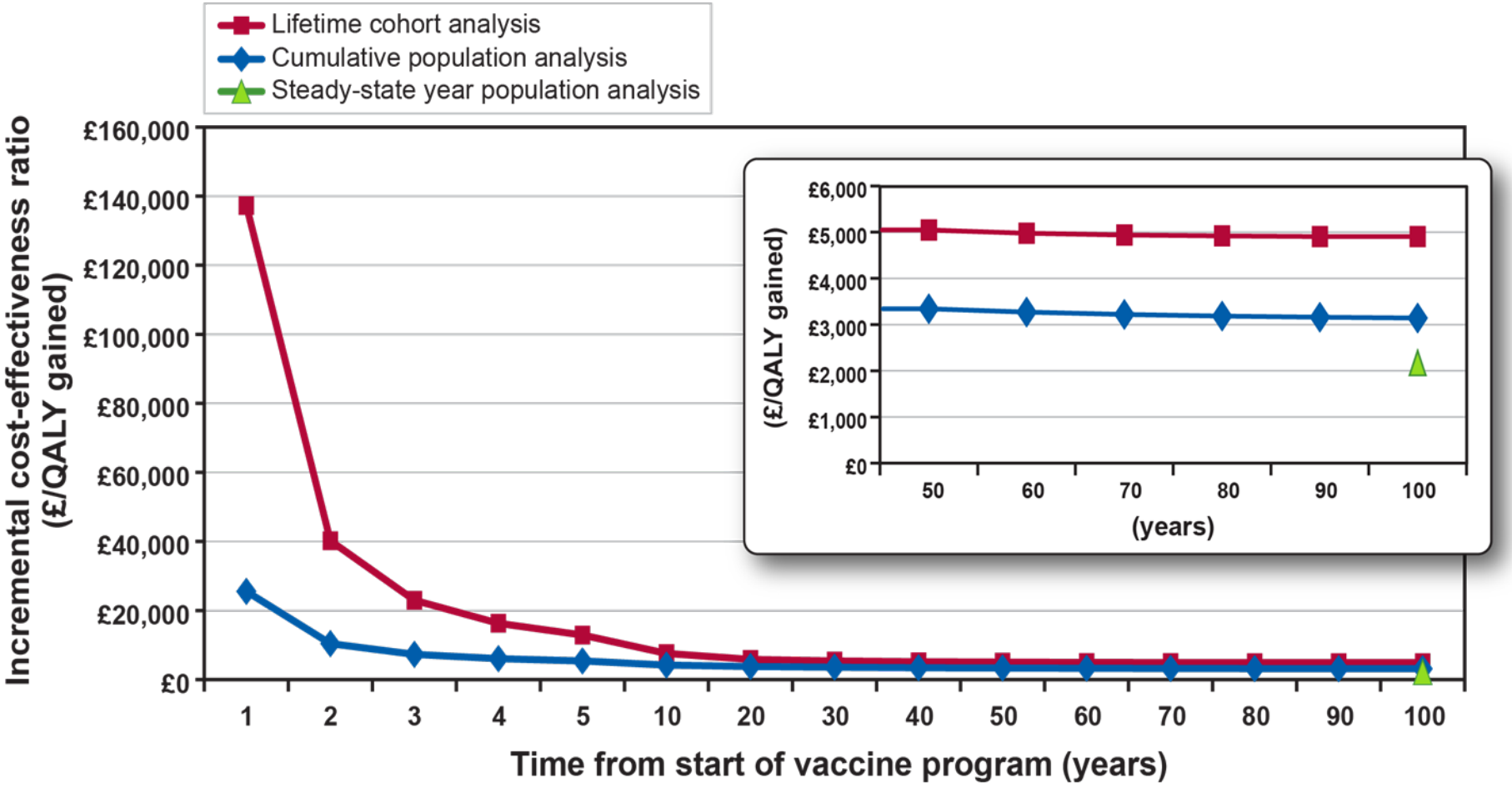
Highest ICER

Parameter (Value in Sensitivity)	ICER (Relative Difference Compared With Cohort Analysis)		
	Cumulative Population Analysis	Steady-state Year Population Analysis	Lifetime Cohort Analysis
Base case*	£3,141 (-36%)	£2,165 (-56%)	£4,904
Cost per case of disease (10x base case)	-£35,028† (+0.3%)	-£28,245† (+20%)	-£35,120
Vaccine cost per course (£200)	£33,194 (-23%)	£24,732 (-42%)	£42,972
Vaccine coverage (95%)	£3,132 (-40%)	£2,456 (-53%)	£5,255
Vaccine efficacy (50%)	£3,935 (-28%)	£4,704 (-14%)	£5,484

Conclusions change based on analysis

ICER = incremental cost-effectiveness ratio (incremental cost per QALY gained).
* Base-case is based on: £39.44 per vaccine course, cost per case of disease ranging by age from £19 to £75, 90% vaccine coverage, and 96% vaccine efficacy.
† Vaccine program costs less and leads to more QALYs (i.e., dominates).

One-Way Sensitivity: Difference in ICERs for Various Time Horizons



Conclusions / Limitations

- Cost-effectiveness estimates using data from dynamic transmission models differ depending on the analytic approach used.
- The two population approaches (cumulative & steady state) yield lower ICERs because they better capture the full population benefit of herd protection (for diseases with positive indirect effects).
- The relative difference in ICERs is large across the 3 analytic approaches.
  - The absolute difference between ICERs may be even larger for diseases where vaccine costs are higher
- Limitations
  - Model included indirect effects of varicella vaccination, such as herd effect and age-shift, but did not include zoster
  - Population parameters, duration of disease, initial force of infection, contact matrix were not varied in sensitivity analysis
  - Systematic sensitivity analyses are difficult for this type of model; uncertainty in the SIR parameters as well as in the CE parameters

Implications for Economic Evaluations of Vaccines

- Economic evaluations of treatments typically require a cost-effectiveness analysis of a representative cohort over a relevant time horizon.
  - For infectious diseases requiring a dynamic transmission model, the impact on a single cohort is not always reflective of the impact on the entire population, particularly in the short-term.
- Cost-effectiveness analyses capturing the cumulative population over time may be most useful for a health care decision maker:
  - Informs budget planning in the short term
  - Provides average cost-effectiveness estimates, including the first years of the vaccine program, where the ICER is changing
  - However, ICERs estimated using the cumulative population approach are not directly comparable to cohort cost-effectiveness analyses
  - Threshold values developed for cohort cost-effectiveness analyses may not apply to population cost-effectiveness analyses

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Back-up Slides

Model Inputs: Who Acquires Infection From Whom (WAIFW) Matrix*

Age/Age	<1	1 to 4	5 to 11	12 to 19	20 to 24	25 to 44	45 to 64	65+
<1	β_{11}	β	β	β	β	β	β	β
1 to 4	β	β_{22}	β	β	β	β	β	β
5 to 11	β	β	β_{33}	β	β	β	β	β
12 to 19	β	β	β	β_{44}	β	β	β	β
20 to 24	β	β	β	β	β_{55}	β	β	β
25 to 44	β	β	β	β	β	β_{66}	β	β
45 to 64	β	β	β	β	β	β	β_{77}	β
65+	β	β	β	β	β	β	β	β_{88}†

*β_{ij} is defined as the rate at which one individual from Age Group *i* comes into *effective* contact with one individual from Age Group *j*.
†The off-diagonal *β*s are all the same as β_{88} creating an assortative WAIFW matrix. The 8x8 matrix combined with the 8x1 vector of initial infectious population and 8x1 vector of initial force of infection are used to solve for the 8 unknown *β*-values. This assortative matrix is based on that used in Brisson & Edmunds, 2000.

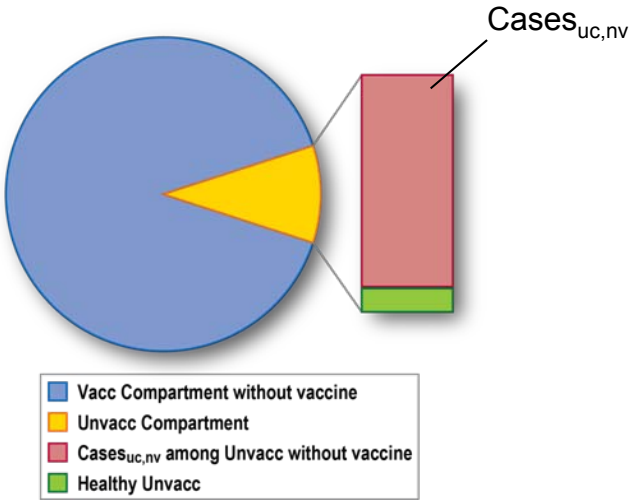
Model Inputs: Initial Force of Infection and Population*†

Age Group	Initial Force of Infection	Initial Susceptible Population	Initial Infectious Population	Initial Recovered Population
<1 year	0.110	696,207	2,793	0
1 to 4 years	0.180	1,423,152	9,826	1,235,123
5 to 11 years	0.150	994,418	5,721	3,302,941
12 to 19 years	0.090	535,547	1,849	4,893,424
20 to 24 years	0.090	205,794	710	3,558,296
25 to 44 years	0.080	323,012	991	14,796,397
45 to 64 years	0.070	68,314	183	13,771,602
65+ years	0.070	4,097	11	8,978,692

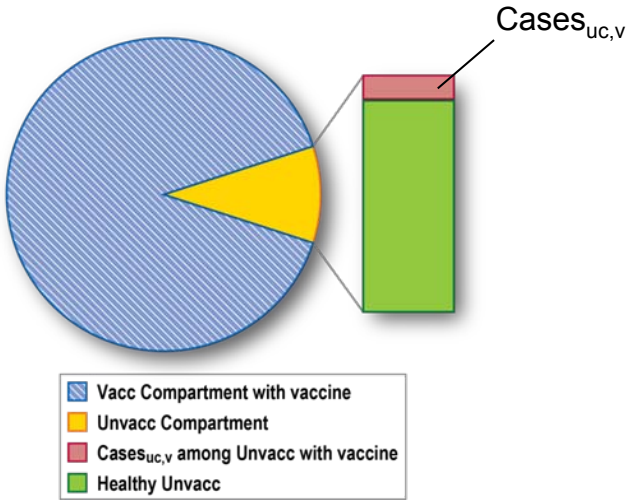
* Force of infection is defined as the annual rate at which susceptible individuals become infectious. Values taken from Brisson & Edmonds, 2001.
† Initial population is based on England & Wales data for 2009 (Office of National Statistics, 2009) and stratified into Susceptible, Infectious, & Recovered compartments in accordance with the method defined by Vynnycky et al., 2010.

Method for Measuring Herd Effect

Sizes of Compartments and Unvaccinated Cases of disease: without Vaccine



Sizes of Compartments and Unvaccinated Cases of disease: with Vaccine (90% Coverage)



- To measure herd effect, we first subdivided the population into 2 groups; those who would receive vaccine and those who would not (Vaccinated and Unvaccinated compartments).
- We then ran the model and tracked cases among those in the unvaccinated compartment without vaccine ($Cases_{uc,nv}$) and in the unvaccinated compartment with vaccine ($Cases_{uc,v}$).
- Herd effect is then calculated according the equation below:

$$HerdEffect = \frac{\left(\frac{Cases_{uc,\,nv}}{Unvaccinated}\right) - \left(\frac{Cases_{uc,\,v}}{Unvaccinated}\right)}{\frac{Cases_{uc,nv}}{Unvaccinated}} = \frac{Cases_{uc,\,nv} - Cases_{uc,\,v}}{Cases_{uc,\,nv}}$$

* The “without vaccine” scenario was *simulated* by setting efficacy to zero to hold the number of people in the unvaccinated compartment constant.

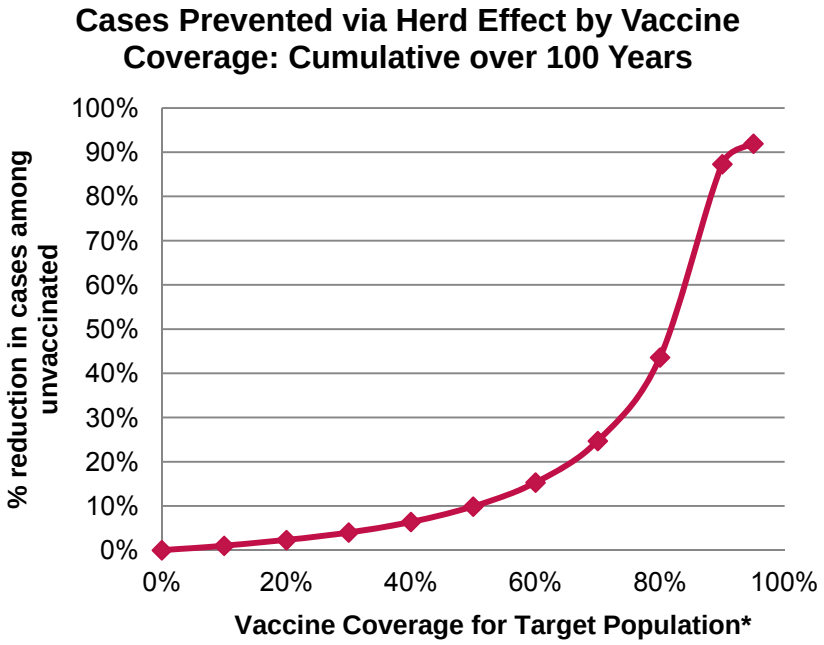
Estimates of Herd Effect: Cumulative Population Analysis, 100 Year Time Horizon, Undiscounted

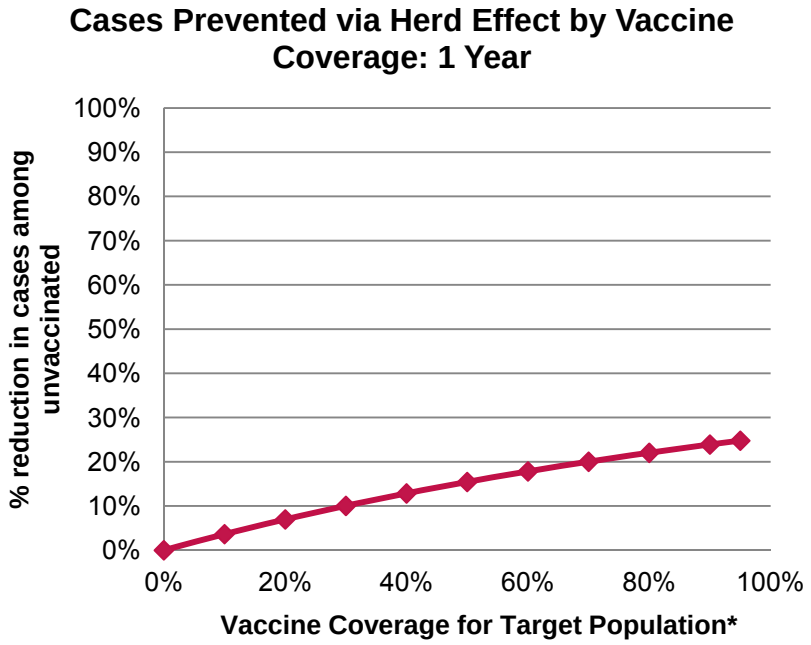
	Entire Population	Vaccinated Group	Unvaccinated Group
Cases, without vaccine*	69,223,820	58,343,600	10,880,220
Cases, with vaccine†	1,390,698	6,578	1,384,120
Cases prevented (% reduction)	67,833,122 (97.99%)	58,337,022 (99.99%)	9,496,100 (87.28%)
Estimated # of cases prevented via direct effect (% reduction)	58,337,022 (84.27%)	58,337,022 (99.99%)	---
Estimated # of cases prevented via herd effect (% reduction)	9,496,100 (13.72%)	---	9,496,100 (87.28%)

- Herd effect is calculated as the % reduction in cases among the unvaccinated population (e.g., 87.28%).

* Estimated by running the model with 0% vaccine coverage.
† Estimated by running the model with 90% vaccine coverage and 96% efficacy.

Estimates of Herd Effect by Vaccine Coverage: Cumulative Population Analysis, in Year 1 and Year 100, Undiscounted





* Vaccine coverage refers to the percent of the birth cohort vaccinated. In year 1, this reflects the percent of the 699,000 newborns vaccinated. By year 100, the model has reached steady-state, and the percentage reflects the percent of the whole population vaccinated.