The impact of increasing vaccine coverage on the distribution of disease:

measles in the UK

W.J. Edmunds[1,2]

Albert Jan Van Hoek[2]

[1]Infectious Disease Epidemiology Unit

London School of Hygiene and Tropical Medicine

Keppel Street,

London WC1E 7HT

United Kingdom

[2]Centre for Infections

Health Protection Agency

61 Colindale Avenue

Colindale, NW9 5EQ

United Kingdom

Abstract

We present a model of the transmission of measles in a Western European country parameterised from recent data on contact patterns, and pre-vaccination serological data (from Denmark). Health outcomes are measured in terms of cases, deaths, complications, and QALYs gained. Data from the US from 1987-2000 are used to estimate complication rates. We use the model to explore the impact of increasing measles vaccine coverage. We note that there is a non-linear relationship between the level of coverage achieved and the benefits of the programme, and that for a 1-dose policy, or a 2-dose policy with low or intermediate levels of coverage increasing coverage further results in increasing marginal returns. This is partly as a result of age-dependency in the risk of infection, and age-dependency in the risk of complications and deaths following measles vaccine coverage. That is, as coverage increases, the average age at infection increases, resulting in fewer cases in young children and therefore fewer QALYs lost. At high levels of coverage with a 2-dose policy there are decreasing marginal returns at levels of immunisation close to the threshold needed for elimination. The incremental benefits of a second dose are smaller than the incremental benefits of a first dose. If coverage is uneven in the population, then increasing coverage in either groups has a similar impact on the overall level of disease in the population. However, increasing coverage in the high-uptake part of the population increases inequalities in health, whereas, increasing coverage in the low-uptake areas decreases health disparities.

1. Introduction

Many immunisation services, such as the UK vaccination programme, are based around the idea of universal coverage. However, this is never achieved in practice. Coverage may be lower in certain ethnic, socio-economic, religious, or geographical groups, or may vary due to the beliefs of the parents of the children concerned. Increasing coverage in these harder-to-reach populations almost certainly comes at an increased cost (though there is little quantitative information on this). Hence, an alternative strategy might be to ensure high coverage in the remainder of the population, reducing disease in the hard-to-reach groups, via indirect protection (herd immunity). This paper explores these issues: under what circumstances is it better to increase coverage in the hard-to-reach groups, and under what circumstances is it better to target resources to the easier to reach sub-populations? We use the example of measles vaccination in the UK, and use a model that is parameterised based on recent European data on underlying contact patterns. There are two scheduled opportunities to receive measles vaccine in the UK, and many other countries: during the second year of life (at around 15 months of age) and at school entry (at around 4 years of age). The secondary aim of this study is therefore to assess the relative benefits of increasing first or second-dose coverage.

2. Methods

2.1 Mathematical model of measles transmission and disease

We adapt a realistic age-structured mathematical model of measles transmission, first put forward by Schenzle [1].The model is adapted to reflect the current UK population structure (data from 2003 is used), and the underlying contact structure is given by a recent survey of contact patterns in UK and seven other European countries [2]. For the purposes of modelling age-specific contact patterns, 10 different age groups were used (<2, 2-4, 4-10,11-16,17-21,22-24,25-34, 35-44, 45-64, 65+), which were chosen to broadly reflect important epidemiological and

educational changes (the younger age groups reflect school and college organisation). The Schenzle model was adapted to reflect a situation of (potentially) heterogeneous mixing across social or geographical groups (i.e. the model is a realistic age structured transmission dynamic meta-population model). For ease of exposition there are only two population groups of equal size, one with higher coverage than the other. For ease of reference the two population subgroups will be referred to as Low (*L*) and High (*H*) to reflect groups with Low and High vaccine coverage. The force of infection (the per-susceptible rate of infection) acting on age-group *i* in sub-group *L* at time *t,* $\lambda_{iL}(t)$, can thus be described as:

$$\lambda_{iL}(t) \quad = \quad \alpha \sum_j \beta_{ij} Y_{jL}(t) + (1-\alpha) \sum_j \beta_{ij} Y_{jH}(t) \qquad (1)$$

where α, which takes a value between 0 and 1, is the amount of within sub-group mixing, β_{ij} is the effective contact rate between susceptibles of age group *i* and infectious individuals of age group *j* (derived from POLYMOD data) and $Y_{jL}(t)$ and $Y_{jH}(t)$ are the numbers of infectious individuals at time *t* in age group *j* and population subgroup *L* and *H* respectively. A similar equation for the High vaccine coverage group is simple to derive. In the initial part of the paper, a value for α of 0.5 was used (implying that the two subgroups mix equally well both within and between each other). Higher values of this parameter are used in the second part of the paper to assess the impact of unequal coverage on subgroups that do not mix homogenously (for instance, a value of 0.8 implies that 80% of contacts are made within an individual's own population subgroup and only 20% of contacts are made outside that group).

We first examine the effect of increasing first and second dose coverage, assuming that the two groups mix freely with each other both within and between groups (effectively this means that there is no difference in coverage between the two

groups, as they are not epidemiologically identifiably different). This model is used to assess the benefits (in terms of long-term reduction both in cases of disease and cases with serious consequences) of increasing coverage. Specifically, the model is used to assess the relative benefits of increasing first and second dose coverage, given that a certain base-line level of coverage has already been achieved.

The model is then extended to reflect a situation in which one group in the population consistently has higher level of coverage than another. The model is then used to assess under which circumstances it is better to increase coverage in the low-uptake group, and when it is best to increase coverage in the high vaccine coverage group.

2.2 Model parameterisation

Rates of measles infection (prior to immunisation)

The pre-vaccination force of infection (the age-dependent risk that susceptibles are infected by measles) was estimated from age-specific pre-vaccination data from Denmark [3]. Denmark was the last country in Western Europe to introduce universal measles vaccination (in 1988), and this serological survey was taken at this time. It therefore represents the most recent data on the epidemiology of measles in Europe in an undisturbed state (though the data is now two decades old). We assume that the age-related patterns of sero-prevalence reflect age-related cumulative exposure, as the system is at endemic equilibrium (that is the incidence is stable through time prior to the introduction of vaccination). Data on the contact patterns among individuals of different ages were collected as part of the POLYMOD project and were used to parameterize the mixing patterns assumed in the model. A general base-case Who-Acquired-Infection-from-Whom matrix (M_{ij}) was derived using all contacts that were reported by the UK study population and a measles-specific transmission coefficient q was estimated by fitting the model to the sero-prevalence

data by maximum likelihood, assuming time-dependent equilibrium. Multiplying M_{ij} by q gives the effective contact rate, β_{ij} (see equation 1) [4]. To take account of uncertainty in the contact patterns and uncertainty in the sero-prevalence data, 1000 bootstrap samples of both were drawn and the fitting repeated to give a bootstrap sample for the resulting β_{ij} matrix.

The best fitting age-specific force of infection, and the resulting fit to the age-serological profile is given in Figures 1a and 1b respectively, along with associated 95% bootstrap confidence intervals. The age-specific proportion sero-positive by age, taken in Denmark just prior to vaccine introduction [3], is also shown in Figure 1b. Note that only those under the age of 18 years were tested in the sero-survey. The force of infection in adults can, however, be derived from the contact pattern, given that q is estimated and assumed to be constant with respect to age. The increased contact that adults aged 25-44 years have with young children results in an increase in the force of infection in these age groups. Note, also that the model produces a slightly higher estimate of the force of infection (or cumulative proportion with evidence of infection) than the data suggest for the youngest age groups. This may be because of changes in mixing patterns over time (that is, children are more likely to attend day-care centres in contemporary Britain than they were in Denmark 20 years ago), giving a higher force of infection than was observed.

Clinical features and complication rates

Not all measles infections are clinically apparent. A review of the literature [5] suggested that 22.5% (range 0-45%) of measles cases did not seek medical attention, and are assumed here to be asymptomatic. The remaining cases are assumed to present with an array of symptoms including rash and fever that typically last 7-10 days. Measles is also associated with a wide array of complications, the

frequency of which varies by age (see later). Amongst the common complications are pneumonia, otitis media, diarrhoea, and febrile seizures. Less common complications include death, encephalitis, and subacute sclerosing panencephalitis, a fatal degenerative neurological disease that is a consequence of persistent measles infection. Case-fatality and complication rates for measles are dependent on socio-economic conditions, and so to estimate the benefits of improving measles coverage in a Western European context requires estimates of these rates to be taken from contemporary sources from developed countries. Perry and Halsey [6] have published a review of the clinical features of over 67,000 measles cases reported to the US Centres for Disease Control and Prevention (CDC) over the period 1987-2000. The data from this review is used to determine age-specific complication and death rates with associated uncertainty. These and other parameters are summarised in Table 1. Figure 2 shows the mean age-specific complication and death rates from this review. Note the typical U shaped curve, with complications being more prevalent in young children and adults.

Health related quality of life detriments for health states associated with measles and measles complications were difficult to identify in the literature. Findings from studies of similar diseases were applied. The QALY loss associated with an uncomplicated measles cases was assumed to be similar to that for chickenpox [7] allowing for the longer duration of illness typical for measles (10 days as opposed to 7 days). The QALY loss associated with diarrhoea was taken from studies of rotavirus gastroenteritis [8], pneumonia and otitis media from studies of pneumococcal disease [9], and acute encephalitis from studies of HIV positive patients with toxoplasma encephalitis [10] (it was assumed to last 1 week). If no measure of statistical variation was provided for these health states, the SD was arbitrarily assumed to equal 0.25* mean, and normal distributions were assumed for the mean QALY losses associated with each state (truncated at zero). Early deaths associated with measles were

assumed to lose the average quality-adjusted life-expectancy for that age, where the life-expectancy was generated from ONS data, and the quality adjustments from a study of the general UK population (we assumed that children had an average utility of 0.9) [11]. A discount rate of 3.5% per annum was used to calculate discounted quality-adjusted life-years lost from early death. The QALYs attributable to rare, but serious long-term sequelae of measles (e.g. from SSPE) were ignored to a lack of data. It is, however, unlikely that this will seriously affect the conclusions of this work, these complications are very rare [5]. The average costs of hospitalised and non-hospitalised measles cases were taken from a recent international review [5]. Costs to the health system were used, and were inflated to 2007 using the Hospital and Community Health Services Pay and Prices Index [12]. All future costs and QALYs gained were discounted at 3.5% (as recommended).

MMR coverage and vaccine efficacy

In England MMR vaccine coverage is recorded routinely at 2 years of age and 5 years of age, by primary care trusts (PCTs), and collated by the HPA. Some children are vaccinated late, so the recorded coverage at 5 years is a better measure of the overall proportion receiving at least one dose, though such data are obviously less contemporaneous (that is most of those having received one dose would have been vaccinated at least 3 years earlier). Recorded coverage at 5 years of age is currently 87% for the first dose and 74% for the second dose. There is considerable geographical variation in this [13]. Reported MMR coverage (measured at 5 years of age) varies between 50% and 95% for the first dose of MMR, and 36% and 90% for the second dose of MMR (based on the 135 PCTs that reported data). Most of the poorly performing PCTs are in London, with an average first dose coverage of 75% (range 50-91%) and an average second dose coverage of 53% (range 36-79%) at 5 years of age (Figure 3). It is uncertain to what extent these figures underestimate vaccine coverage due to programmatic difficulties (changes in child health computer

systems etc), and private provision of measles vaccine (partly as a result of concerns about the safety of MMR some parents opted to use single antigen measles vaccine, which would not be recorded in these data). We use these data as a guide, and explore the impact of increasing measles vaccine coverage from 50% to 100% (first dose and second dose). Although there is variation in the timeliness of measles vaccine delivery, we assume that these doses are all given at 18 months or 4 years of age for the first and second doses respectively. We assume, that only those receiving the first dose receive a dose at the second opportunity (at 4 years), We relax this assumption for specified simulations, and assume that there is no correlation between those receiving vaccine at the first and second opportunities (that is, that it is random).

Most estimates of measles vaccine efficacy in developed countries suggest that a single dose given in the second year of life provides long-term (probably lifelong) protection to over 90% of vaccinees [14-15], and that two doses offers approximately 99% protection [15], although lower estimates of efficacy are apparent in the literature [16]. We assume that the each dose provides complete protection for 90% of those that receive it and are susceptible. Vaccination of infected or immune individuals has no effect.

3. Results

3.1 Increasing first or second dose vaccine coverage

Figure 4 shows the estimated long-run number of cases, complications deaths and QALYs lost, resulting from a single dose strategy at different levels of vaccine coverage. It is clear that there is a roughly inverse linear relationship between coverage and the incidence of infection (and therefore clinical cases), as would be expected from the solution to the homogenously mixed version of this model (see, for

instance, [17]). The relationships are not exactly linear, however, due to the increase in the age at infection following vaccination (both the force of infection and the likelihood of developing severe disease following infection are dependent on age (Figures 1 and 2 respectively)).

The addition of a second dose clearly reduces the incidence further, though the additional benefits are small. Figure 5 shows the incremental benefits (in terms of both QALYs gained and treatment costs avoided) from increasing coverage by 10%, according to the base-line coverage. The dotted lines are for a 2-dose policy and the solid lines are for a single dose policy. Note that the second dose is assumed to be given at the same level of coverage as the first dose, and an increase in a 2-dose policy between (say) 30% and 40% coverage involves the use of twice as much vaccine as an increase from 30% to 40% coverage of a single dose policy. It is clear that there are increasing marginal returns derived from increasing measles coverage until very high levels of coverage are achieved. At these levels of coverage (around 90%+), there is decreasing marginal returns, such that increasing coverage by a fixed amount (10% in this case for both doses) results in decreased additional benefits. At levels of coverage over the threshold for elimination there are no additional long-run benefits derived from further increases in coverage (not apparent from figure 5).

3.2 Unequal coverage by population subgroup

If coverage is unequal, then should efforts be put into increasing vaccine uptake in the low coverage area, or increasing uptake in the higher coverage area, with the aim of protecting the low-coverage area indirectly? Figure 6 shows the estimated long-run impact of increasing coverage in the high coverage area (left hand side) or the low coverage area (right hand side). In both cases the starting level of coverage is 50% in the low uptake area and 70% in the high uptake area. The green lines give the

number of QALYs lost in the low uptake area, the red lines the number of QALYs lost in the high uptake area, and the blue lines are the sum of the overall QALYs lost . The solid lines are for the situation when the two areas mix freely with each other, and the dotted and dashed lines are when 75% or 95% of mixing is within-group respectively (the remainder of contacts being made with the other group). Clearly increasing coverage in the high uptake area improves the health of this sub-population, and to a lesser extent that of the low uptake group, leading to increasing health disparities between the two sub-populations (Figure 6). Increasing coverage in the low coverage area, on the other hand, leads to reducing health inequalities (until coverage in the "low" area exceeds that in the "high" area). If mixing is more assortative (like-with-like), then the smaller is the impact on the other group of increasing coverage in one of the groups. When mixing is random between the subgroups, then increasing coverage in one of the subgroups has the same impact on both subgroups. When mixing is assortative, then the increase in health derived from increasing coverage in the low risk groups is slightly greater than the increase derived from targeting the low risk group, though the differences are very marginal.

4. Discussion

We have used a model of measles infection and disease to assess the impact of changes in coverage on the long-run outcome of disease. The results suggest that there may be increasing marginal returns at low to intermediate levels of coverage, but that as the level of immunisation approaches the threshold for elimination, then the additional benefits gained from increasing coverage fall away. The increasing marginal returns arise, in part, from the increase in the average age at infection following immunisation, from infancy into early to middle childhood. (Further increases in average age will increase the adults contracting measles (as a proportion of all measles cases) and therefore the average severity of cases.) In general, greater benefits arise from increasing first dose coverage, as opposed to

second dose coverage. This is because susceptibility is maximised at the younger ages, and a fraction of those given a second dose are already immune, either from previous vaccination, or from infection. If the population is stratified into groups which differ in their vaccine uptake rates, then the model suggests that the overall health benefits arising from either targeting the high or low uptake groups are similar, though targeting the low-coverage groups will serve to reduce health inequalities.

The model was parameterised using contemporary contact pattern data, and pre-vaccination serological data from the last country in Western Europe to introduce measles vaccination (Denmark). The likelihood of complications following apparent measles infection is taken from a large study of measles cases reported to CDC over the period 1987-2000. The model is therefore parameterised from high-quality contemporary data from industrialised countries, and is therefore an improvement on other measles models available in the literature [1,3,17-19]. There are, however, a number of drawbacks to the data used. The serological data are two decades old, and mixing patterns may have altered over this period (indeed, the model tends to overestimate the force of infection in the youngest ages, perhaps due to an increase in contact amongst these age groups due to increasing use of child-care). Furthermore, the data on complications are based on reported cases, and may, therefore, overestimate the complication rate, if the most sick individuals are more likely to be reported. On the other hand, we assumed that those infected individuals who are not in contact with the health services do not suffer any adverse health consequences (i.e. have no QALY loss) due to their measles infection (in essence we assume that they are asymptomatic), though this seems unlikely to be the case.

To keep analysis reasonably straightforward, the results are presented in terms of the equilibrium impact (i.e. the long-run impact on the distribution of disease in the community, as a result of a change in the immunisation coverage level). In reality it

may take many years for these changes to unfold. As the dynamics may have an important bearing on the cost-effectiveness of changes to the programme, the results (as presented here) can only be used to calculate the cost-effectiveness of changes to immunisation coverage if these changes are small (so the system is assumed to move rapidly to the new equilibrium).

The second dose is modelled here as a second dose – that is, only those that received the first dose, receive a second one at four years of age. This underestimates the effectiveness of the second opportunity, as some children will receive their first dose at this age. To obtain a more accurate assessment of the effectiveness (and cost-effectivness) of the second opportunity, further work is needed to establish what proportion of children receive a first dose at this age. Nevertheless the results presented here are a reasonable description of the (lon-run) effectiveness of a second *dose*. That is, as approximately 90% of those who are vaccinated with measles containing vaccine are immunised after a single dose, the second dose is far less effective (by an order of magnitude) than the first. The second dose may well, however, represent a worthwhile public health investment as the burden of measles is high in the absence of good control, and the costs of the vaccination programme comparatively low. Further work is underway to establish this.

As with all modelling studies, the results of these analyses are contingent on the assumptions inherent in the model. We have adapted a well-used model of measles, and used contemporary parameter values estimated from developed countries. Although a number of uncertainties remain, we believe the results presented here give a reasonable basis on which to make decisions about improvement of measles (or MMR) vaccine coverage in industrialised countries.

5. Acknowledgements

The study was part-funded by the National Institute of Health and Clinical Excellence (WJE) and the European Commission (AJvH, POLYMOD Contract number: SSP22-CT-2004-502084). We thank POLYMOD for the contact pattern data.

6. References

[1] Schenle D. An age structures model of pre- and post-vaccination measles transmission. IMA J Math Appl Med Biol. 1984;1(2):169-91

[2] Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, Massari M, Salmaso S, Tomba GS, Wallinga J, Heijne J, Sadkowska-Todys M, Rosinska M, Edmunds WJ. Social contacts and mixing patterns relevant to the spread of infectious diseases.PLoS Med. 2008 Mar 25;5(3):e74.

[3] Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H; ESEN Project. European Sero-epidemiology Network. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. Epidemiol Infect. 2000 Dec;125(3):635-50.

[4] Wallinga J, Teunis P, Kretzschmar M.Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents.Am J Epidemiol. 2006 Nov 15;164(10):936-44. Epub 2006 Sep 12.

[5] Carabin H, Edmunds WJ, Kou U, van den Hof S, Nguyen VH. The average cost of measles cases and adverse events following vaccination in industrialised countries.BMC Public Health. 2002 Sep 19;2:22. Epub 2002 Sep 19.

[6] Perry RT and Halsey NA. The clinical significance of measles. J Infect Dis. 2004 May 1;189 Suppl 1:S4-16.

[7] Brisson M, Edmunds WJ.Varicella vaccination in England and Wales: cost-utility analysis.Arch Dis Child. 2003 Oct;88(10):862-9.

[8] Jit M, Edmunds WJ.Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination.Vaccine. 2007 May 16;25(20):3971-9. Epub 2007 Mar 13.

[9] Melegaro A, Edmunds WJ.Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales.Vaccine. 2004 Oct 22;22(31-32):4203-14.

[10] Yazdanpanah Y, Goldie SJ, Paltiel AD, Losina E, Coudeville L, Weinstein MC, Gerard Y, Kimmel AD, Zhang H, Salamon R, Mouton Y, Freedberg KA.Prevention of human immunodeficiency virus-related opportunistic infections in France: a cost-effectiveness analysis.Clin Infect Dis. 2003 Jan 1;36(1):86-96. Epub 2002 Dec 11.

[11] Kind P, Dolan P, Gudex C, Williams A.Variations in population health status: results from a United Kingdom national questionnaire survey.BMJ. 1998 Mar 7;316(7133):736-41.

[12] Curtis L. Unit costs of health and social care 2007. PSSRU, University of Kent.

[13] http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1211441442288

[14] Marks JS, Halpin TJ, Orenstein WA. Measles vaccine efficacy in children previously vaccinated at 12 months of age. Pediatrics. 1978 Dec;62(6):955-60

[15]. Janaszek W, Gay NJ, Gut W.Measles vaccine efficacy during an epidemic in 1998 in the highly vaccinated population of Poland.Vaccine. 2003 Jan 17;21(5-6):473-8.

[16] Eichner M, Diebner HH, Schubert C, Kreth HW, Dietz K. Estimation of the time-dependent vaccine efficacy from a measles epidemic. Stat Med. 2002 Aug 30;21(16):2355-68

[17] Anderson RM and May RM Infectious diseases of humans: dynamics and control. Ozford University Press, Oxford. 1991.

[18] Paulo AC, Gomes MC, Gomes MG.Dynamics and control of measles in Portugal: accessing the impact of anticipating the age for the first dose of MMR from 15 to 12 months of age.Vaccine. 2008 May 2;26(19):2418-27. Epub 2008 Mar 19

[19] MacIntyre CR, Gay NJ, Gidding HF, Hull BP, Gilbert GL, McIntyre PB.A mathematical model to measure the impact of the Measles Control Campaign on the potential for measles transmission in Australia.Int J Infect Dis. 2002 Dec;6(4):277-82.

7. Tables

Table 1: Parameter values used in the model

Disease outco	Clinical diseas	Death	Diarrhoea	Encephalitis	Otitis me	Pneumonia	Hospitalisa	Any
<5yrs	77.5%	0.3%	10.4%	0.1%	12.6%	7.9%	20.9%	29.0%
5-9 yrs	77.5%	0.3%	5.6%	0.1%	4.2%	3.0%	8.7%	15.3%
10-19 yrs	77.5%	0.1%	3.3%	0.1%	1.8%	1.8%	8.0%	11.7%
20-29 yrs	77.5%	0.3%	7.6%	0.2%	1.7%	5.6%	18.5%	22.4%
30+ yrs	77.5%	0.7%	9.2%	0.2%	2.0%	8.4%	21.8%	25.4%

QALY loss	General Meas	Death	Diarrhoea	Encephalitis	Otitis me	Pneumonia		
<5yrs	0.005343852	23.55	0.002024	0.0057374	0.00616	0.006151		
5-9 yrs	0.005343852	23.00	0.002024	0.0057374	0.00616	0.006151		
10-19 yrs	0.005343852	22.00	0.002024	0.0057374	0.00616	0.006151		
20-29 yrs	0.005343852	20.45	0.002024	0.0057374	0.00616	0.006151		
30-44	0.005343852	17.78	0.002024	0.0057374	0.00616	0.006151		
45-64	0.005343852	12.51	0.002024	0.0057374	0.00616	0.006151		
65+	0.005343852	3.04	0.002024	0.0057374	0.00616	0.006151		

Costs	£
Measles case	195.22
Hospitalisation	1220.182

8. Figure Legends

Figure 1: Best-fitting estimate of (a) the force of infection and (b) % seropositive with respect to age in the absence of vaccination. 95% bootstrap confidence intervals are shown. The seroprevalence data (b) are from Denmark in 1988.

Figure 2: Age-specific complication and death rates from measles, as reported to CDC 1987-2000 (Perry and Halsey 2004). Deaths and encephalitis are shown on the right-hand axes.

Figure 3. Reported first and second dose MMR coverage by PCT in England. Coverage measured at 5 years of age. Data from Jan-March 2008 (www.hpa.org.uk). Dotted line shows line of equality.

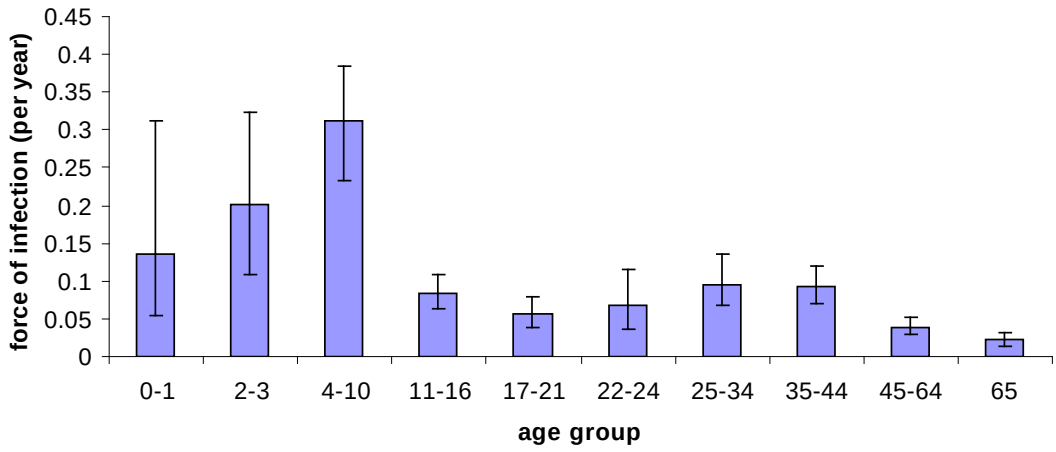
Figure 4. Estimated long-run incidence of clinical cases, complications (severe cases), deaths and QALYs lost resulting from a one-dose measles immunisation policy at different levels of coverage. Results are for a population of 100,000 individuals. Clinical outcomes are shown undiscounted, QALYs are discounted at 3.5% per annum.

Figure 5. Estimated incremental long-run benefits in terms of discounted QALYs gained (right hand axis) and treatment costs avoided (left hand axis) from increasing vaccine coverage by 10% from an initial level of coverage (shown on horizontal axis). Model results are shown for both a one-dose policy (solid lines) and two-doses (dotted lines). Coverage of the second dose is assumed to be equal to coverage of the first dose. An increase in coverage of a 2 dose policy results in twice the use of additional vaccine to the equivalent increase in 1-dose coverage. Results are for a population of 100,000 individuals.

Figure 6. Estimated equilibrium impact (on QALYs lost) of increasing coverage in either a high-coverage area (left hand side) or a low coverage area (right hand side). The initial distribution of coverage is 50% and 70% in the low and high coverage areas respectively. The solid lines are for the situation in which mixing is random between the two groups ($\alpha = 0.5$) and the dotted and dashed lines are for increasing

degrees of assortative mixing (α = 0.75 and 0.95 respectively). The dark green lines are the low coverage area, and the red lines the high coverage area, the blue lines give the overall QALYs lost. The population of both areas is 100,000. Single dose policy only.

Figure 1.


force of infection (per year)
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0-1
2-3
4-10
11-16
17-21
22-24
25-34
35-44
45-64
65
age group

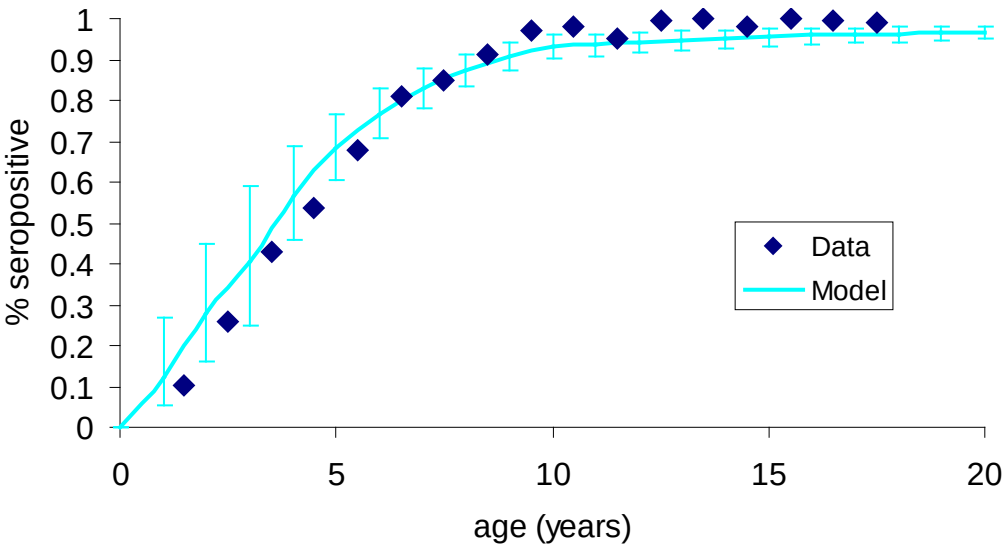

% seropositive
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
age (years)
Data
Model

Figure 2.

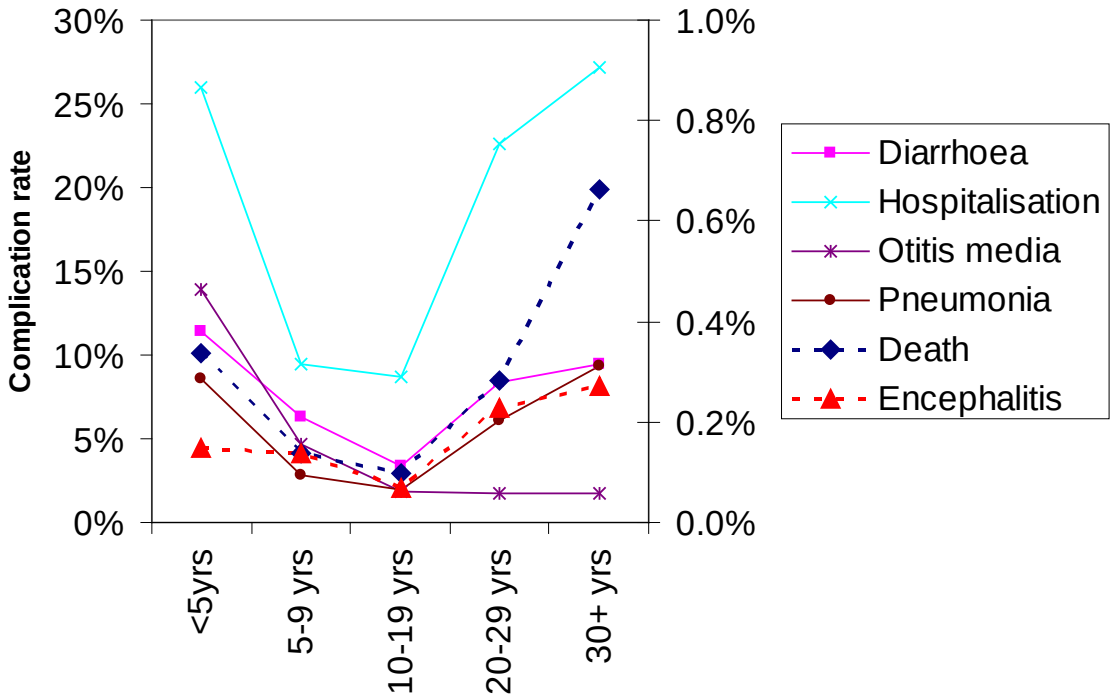

30%
25%
20%
15%
10%
5%
0%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
Complication rate
<5yrs
5-9 yrs
10-19 yrs
20-29 yrs
30+ yrs
Diarrhoea
Hospitalisation
Otitis media
Pneumonia
Death
Encephalitis

Figure 3.

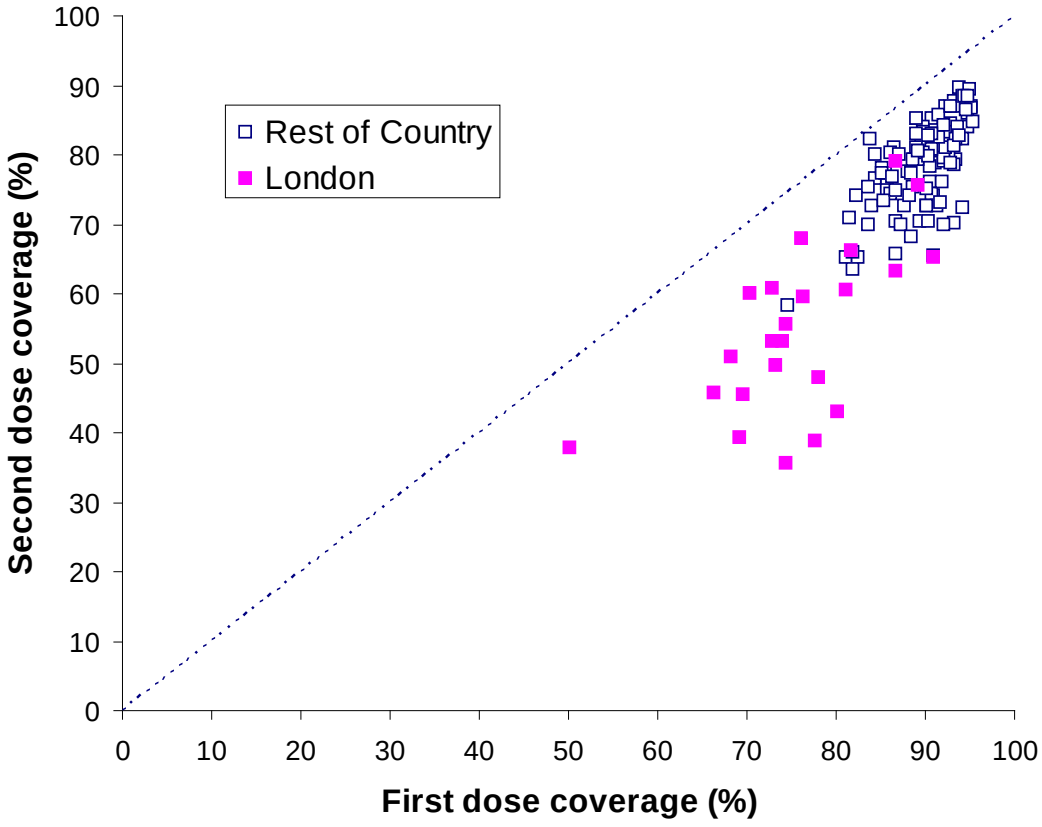

Rest of Country
London
Second dose coverage (%)
First dose coverage (%)
0
10
20
30
40
50
60
70
80
90
100

Figure 4.

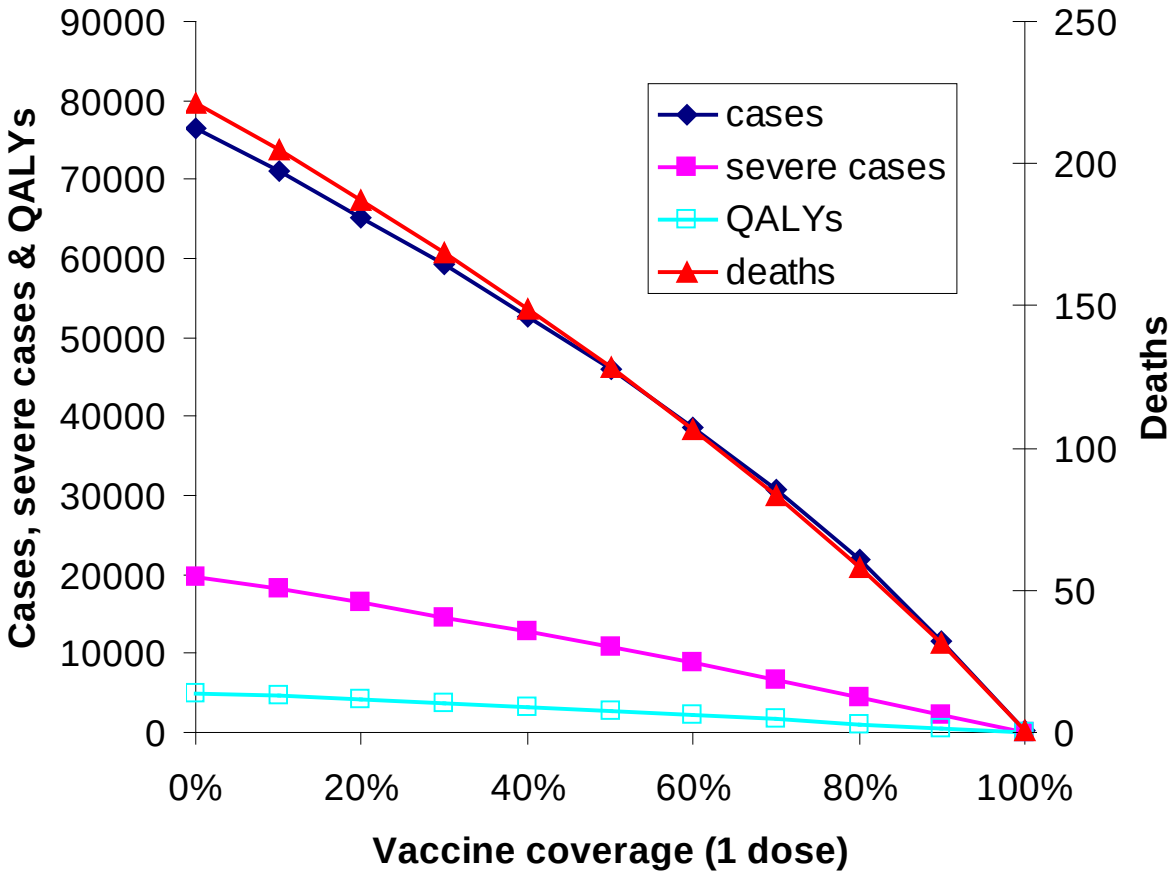

90000
80000
70000
60000
50000
40000
30000
20000
10000
0
Cases, severe cases & QALYs
250
200
150
100
50
0
Deaths
cases
severe cases
QALYs
deaths
0%
20%
40%
60%
80%
100%
Vaccine coverage (1 dose)

Figure 5

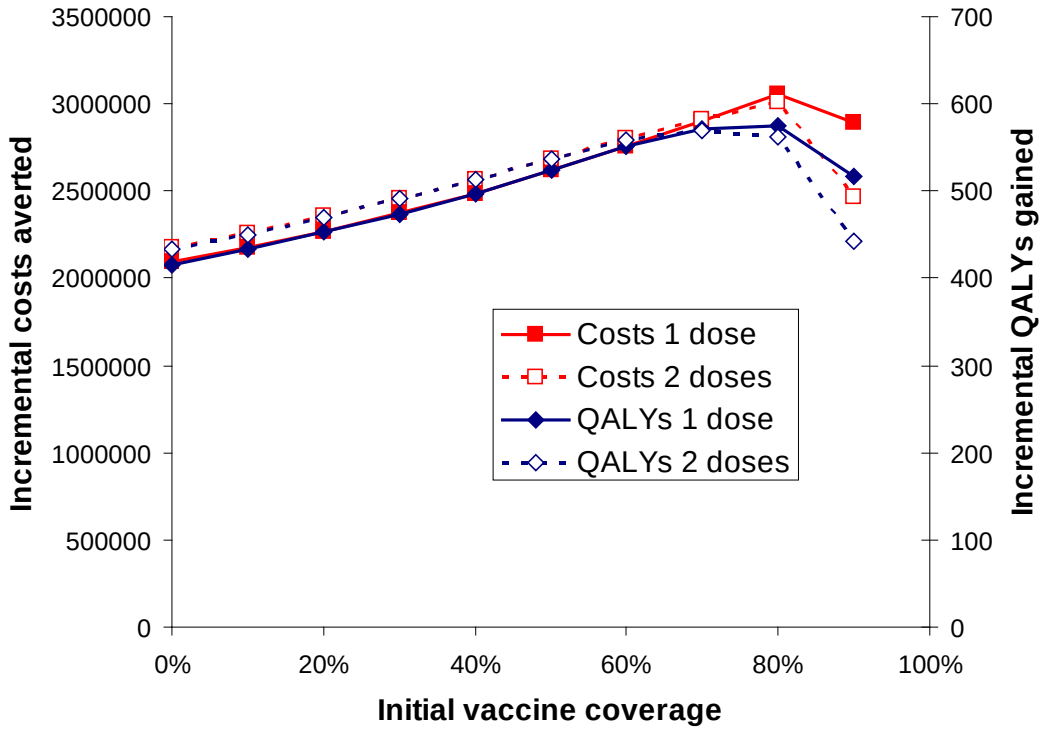
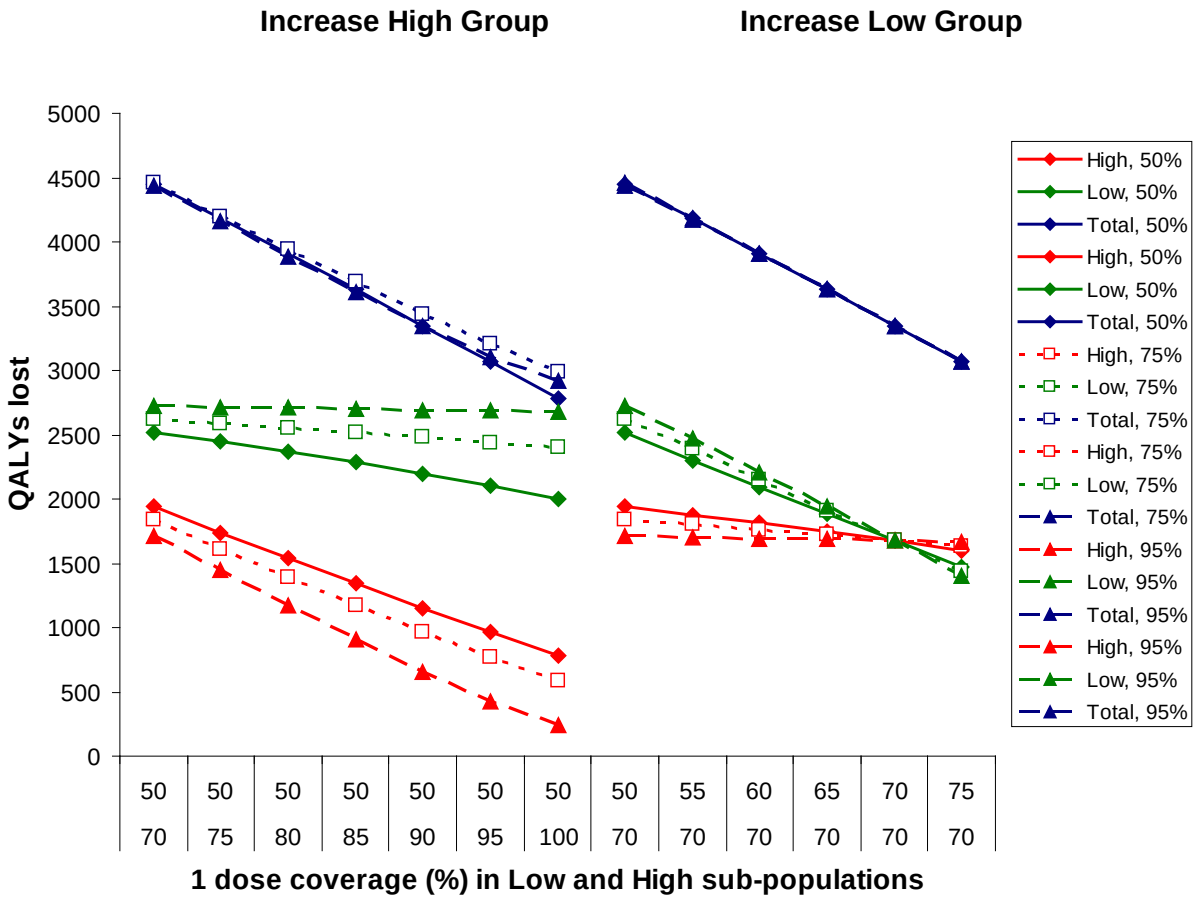

3500000
3000000
2500000
2000000
1500000
1000000
500000
0
Incremental costs averted
700
600
500
400
300
200
100
0
Incremental QALYs gained
0%
20%
40%
60%
80%
100%
Initial vaccine coverage
Costs 1 dose
Costs 2 doses
QALYs 1 dose
QALYs 2 doses

Figure 6


Increase High Group
Increase Low Group
QALYs lost
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
50 50 50 50 50 50 50 50 55 60 65 70 75
70 75 80 85 90 95 100 70 70 70 70 70 70
1 dose coverage (%) in Low and High sub-populations
High, 50%
Low, 50%
Total, 50%
High, 50%
Low, 50%
Total, 50%
High, 75%
Low, 75%
Total, 75%
High, 75%
Low, 75%
Total, 75%
High, 95%
Low, 95%
Total, 95%
High, 95%
Low, 95%
Total, 95%