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Title: Cost-effectiveness and programmatic benefits of maternal vaccination against pertussis in England.

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Abstract: Background:
Maternal pertussis immunisation was introduced during the pertussis resurgence in England in 2012 as a temporary measure to protect infants too young to be vaccinated. The programme was shown to be safe and highly effective. However, continuation of maternal vaccination as a routine programme requires a cost effectiveness analysis.

Method:
The estimated prevented disease burden among mothers and their infants was obtained assuming 89% (95% CI: 19%-99%) vaccine efficacy for mothers and 91% (95% CI: 84%-95%) for infants. Future incidence was projected based on the disease rates in 2010-2012, including the four-year cycle of low and high incidence years. Full probabilistic sensitivity analysis was performed for different scenarios.

Results:
Assuming a vaccine coverage of 60%, there were 1650 prevented hospitalisations in infants (3.5% discounting, the first 10 years), including 55-60 deaths and ~20,500 cases among mothers, of which around 1800 would be severe. The annual costs of the programme are £7.3 million assuming a price of £10 per dose and £9.4 million assuming £15 per dose. Using discounting of 3.5%, a 200 year time horizon and a price of £10 per dose (+ £7.5 administration costs) only 25% of the iterations were below £30,000 per QALY. Using a 35% higher incidence resulted in 88% of the scenarios below this threshold. Assuming that the incidence remains at the level at the height of 2012, then the programme would be highly cost effective, with an ICER of £16,865 (£12,209-£25,976; price of £10 and 3.5%/3.5% discounting).

Conclusion:

Maternal vaccination is effective in preventing severe illness and deaths in infants but the cost-effectiveness of the programme is highly dependent on future incidence which is necessarily uncertain. However, the duration and magnitude of protection against transmission afforded by the current acellular vaccines is also uncertain as are the associated effects on future herd immunity. The direct protection offered by the maternal dose provides the only certain way of protecting vulnerable infants from birth.

Dear Editor,

The manuscript we present is on maternal pertussis vaccination; maternal vaccination was introduced in England to mitigate the observed increase in pertussis in 2012. The programme was initially introduced without much direct evidence, but was very effective.

We present a cost-effectiveness study based on the observed incidence and vaccine-efficacy in England. The future incidence of pertussis is projected including cyclical patterns and both the impact on mother and child. This approach enabled to investigate relevant implications of different discount and time horizon scenarios, as well as the relevant uncertainty.

However most importantly, as you will see in the discussion, the continuation of the programme, whose dramatic success in terms of infant cases and deaths prevented has galvanised global interest [see for example: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM474285.pdf) is threatened by being considered not cost effective. While the decision body in the UK (Joint Committee for Vaccination and Immunisation) has deferred the decision about discontinuing the programme for 5 years, as there was natural concern about letting infants die from a vaccine preventable disease based on cost effectiveness criteria alone. In our discussion we challenge the application of conventional incremental cost effectiveness analyses to this programme and highlight other very tangible benefits that accrue from its implementation. Moreover, the programme is cost effective in epidemic years which raises interesting questions about whether it is feasible to turn it on and off depending on incidence as is currently done with antivirals for influenza.

As other countries are now actively promoting maternal pertussis immunisation but like the UK will need to consider cost effectiveness – even WHO through its Strategic Advisory Group of Experts requires cost effectiveness analyses to support its global recommendations. Ours is the first such analysis of an implemented programme and the methodological, practical, and ethical issues we identify are applicable for other countries and are likely to engender debate (and could be a suitable topic for a commentary).

We therefore hope that you consider this manuscript for review in your journal. The manuscript is not submitted elsewhere.

Yours sincerely,

Albert Jan van Hoek (on behalf of the co-authors)

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Yours faithfully,

Albert Jan van Hoek

Cost-effectiveness and programmatic benefits of maternal vaccination against pertussis in England.

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Abstract

Background:

Maternal pertussis immunisation was introduced during the pertussis resurgence in England in 2012 as a temporary measure to protect infants too young to be vaccinated. The programme was shown to be safe and highly effective. However, continuation of maternal vaccination as a routine programme requires a cost effectiveness analysis.

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Words: 319

Highlights (for review)

- Maternal pertussis vaccination is highly effective at preventing infant deaths
- Its cost-effectiveness as an adjunct to paediatric vaccination needs evaluation
- Future pertussis incidence is the major determinant of cost-effectiveness
- The ability of acellular vaccines to control transmission is questionable
- Given this uncertainty continuation of maternal immunisation is advisable

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Introduction

In October 2012 a maternal pertussis vaccination programme was introduced in England [1] as an outbreak measure in response to the highest number of infant cases and deaths from pertussis in more than a decade in 2012. All of the infants who died developed disease before they were eligible to receive the primary course of vaccine. The maternal programme has been well received in England, with uptake peaking at 60% and evidence of a direct impact in infants under 3 months of age [1].

Maternal vaccination is offered in every pregnancy, ideally between 28 and 32 weeks, but up to 38 weeks [1] and works in two ways: by passive immunisation of the infant through the transport of antibodies across the placenta and by directly protecting the mother which lowers the probability of her being a source of infection to her infant. The programme effectiveness against infant disease has been estimated to be 91% (84%-95%) in England [1] Maternal vaccination thus offers a safe [2] and effective way of directly protecting those too young to be vaccinated.

Although this programme was introduced as a temporary outbreak response measure, the question now is whether, based on the evidence of effectiveness, maternal vaccination should be added to the routine programme in England. In the England, policy recommendations by the Joint Committee and Vaccination and Immunisation require evidence of cost effectiveness.

In this paper we investigate the cost-effectiveness of introducing maternal vaccination programme into the national immunisation schedule, offering a dose to women in every pregnancy.

Methods

Programme under consideration

The programme under study in this analysis is vaccinating pregnant woman in the 3rd trimester with one dose of a pertussis-containing vaccine designed for adult boosting. In practice, women will be offered vaccine at the first appointment in the 3rd trimester (week 28-32, where possible and up to 38 weeks).

Impact of the vaccine

The duration and type of protection induced in the mother and infant differs. The infant is passively protected by maternal antibodies until development of active immunity following receipt of the first dose of pertussis-containing vaccine at 2 months of age. In this analysis disease up to three months of age was considered preventable by maternal vaccination assuming that those hospitalised between two and three months are either still unvaccinated, or were exposed before they could develop protective antibodies after the first dose of the primary course. Vaccinating the mother, will boost her pre-existing immunity which will afford protection for a longer time. This was assumed to be 5 years, based on estimates of the duration of protection after a 5th dose of acellular vaccine given around five years of age and antibody persistence after an adolescent acellular booster [3]. However, pertussis antibody titres rapidly decline within a year of boosting [4] and therefore vaccine is recommended in each pregnancy, regardless of vaccine history in order to passively protect the infant. This means that some women will get pregnant again and receive the vaccine for a second time while still protected against disease. Therefore, to take this into account, the effective duration of maternal protection was reduced. Where vaccine recipients do not become pregnant again they enjoy five years of protection; when they do have a subsequent pregnancy an average interval between pregnancies was assumed of 3 years based on national maternity data [5]. For the analysis a weighted average duration was calculated based on the observed distribution of first, second, third

and fourth pregnancies (see the online material for more detail). The average duration of protection was estimated as 3.89 years or 47 months.

Therefore, for example, if a mother was vaccinated in the 5th month of the programme two months before delivery, disease in the mother would be on average prevented from month 5 until month 52 and in the infant from month 7 until the end of month 9 of the programme.

The preventable disease burden

The transmission of pertussis is cyclical, with a 3-4 year interval between high transmission years. Due to the fluctuating disease burden the cost effectiveness of a dose will change over time within the cycle. Therefore the programme was evaluated over a longer period, using a fluctuating monthly incidence. The fluctuation was simulated by a sine-function with a peak every 4 years, oscillating between the maximum and minimum incidence.

As the vaccine prevents both disease in the infant and the mother, separate estimates of the preventable disease burden were made. For infants under 3 months, the burden of disease was estimated from hospital admission data as pertussis at this age is severe and over 90% of cases require in-patient care [6]; it is also the most complete data source as admissions in infants under 3 months are nearly double the number of notified cases in this age group [6]. In contrast, pertussis in adults is often a mild, unrecognised illness so notifications and laboratory confirmed cases will substantially underestimate the true burden of clinical illness; it is conservatively assumed that laboratory confirmed cases comprise only a third of all clinically significant pertussis illness in adults [7]. Evidence suggests that the source of infection for most infant pertussis cases is other family members [8] so it can be assumed that the exposure in mothers and infants is similar resulting in a synchronised cyclical pattern of infection in both groups.

The future incidence of pertussis is uncertain given the recent resurgence in the UK and some other countries, possibly associated with more rapid waning of immunity after immunisation with acellular than whole cell vaccine [3,9]. Several future incidence scenarios are therefore presented – a low, base case and a high incidence scenario. A low incidence scenario based on 75% of the cases observed in 2012, a base case scenario assuming outbreak sizes as observed in 2011-2012 and three high incidence scenarios, one with 35% more disease than in 2012 in the peak years, a second with 35% higher incidence in the low years, and a third with both a higher incidence in the peaks and troughs. These incidence scenarios were used in combination with different scenarios on the time-horizon and discounting.

Disease outcomes

Infants:

The sine function was fitted using the overall incidence of hospitalised disease in infants under 3 months between September 2010-September 2012. The incidence in the trough year was based on the observed number of hospitalised infant cases in 2010.

Hospitalisation

Infants were admitted to hospital and could have 1 day of admission, multiple days of admission without intensive care, multiple days with intensive care, and multiple days with intensive care and extracorporeal membrane oxygenation (ECMO), for a proportion of intensive care patients special transport was needed.

The duration of admission and whether there was an admission to the paediatric intensive care unit (PICU) was based on the Hospital Episode Statistics (HES) for the period January 2007-February 2012, HES is a database that includes all hospital admissions in England [10] The admission rate to PICU is assumed to be the proportion of patients who needed ventilation (procedure codes OPCS4 E85, E89, X58 and X52). The duration of admission to the PICU and whether ECMO or special transport

was needed was based on the Paediatric Intensive Care Audit Network (PICAnet) database (2006-2012) which contains detailed information on PICU admissions.

The costs were based on the NHS reference costs 2012-2013 [11], using PA65A (Non-elective Upper respiratory Tract Disorder £422 (£282-£523) for those admitted without an overnight stay and PA65B (Non-elective Long stay Upper respiratory Tract Disorder with complications; £758 (£552 – £885) per day) for non-ICU days in case of overnight stay and XB04Z (Pediatric Critical Care Intensive Basic Enhanced; £2,110 (£2,004-£2,130) per day) or XB01Z (Pediatric Critical Care Intensive – ECMO/ECLS; £4,391 (£3,966-£4,763) per day in case of PICU admission without or with ECMO respectively.

Mortality

Although previously it was suggested that the number of pertussis deaths were substantially underestimated [12], a more recent analysis showed that the reporting of deaths was consistent between various sources and that therefore the under reporting of recognised pertussis deaths in England is small [13]. There were 16 reported deaths due to pertussis in infants under 3 months of age born between 1 October 2011- 30 September 2012 (before the maternal programme was introduced) and a total of 513 reported hospitalisations in infants under 3 months in the same period giving a case fatality rate of 3.1% (95% CI: 1.75%-4.7%).

The total utility loss for a fatal case was calculated based on the estimated life expectancy with a correction for the population norms of the quality of life by age. The life expectancy was based on the 2008-2010 mortality [14] and the population norms were obtained from a 2010 survey among 22,166 adults age 16 and over using the SF-6D; for those younger than 16 a population norm of 0.9 was assumed [15].

Adults

For adults, estimations were made for reported and non-reported disease burden which followed the same sine function as in the infants. In the peak month of 2012 the incidence in infants under 3 months was 43.3 per 100,000. Hence assuming a similar incidence in adults the estimated number of infections among the 9,569,461 women aged 20-44 in the population in the peak month was 95.69*43.3 per 100,000 = 4,144. In the peak month there were 365 laboratory confirmed cases among women aged 20-44, therefore 8.8% (365/4,114) of the infections among women are believed to be laboratory confirmed.

Public Health England performed a patient survey to estimate the loss in quality of life due to pertussis as well as the related health care costs [16]. Two groups of patients were recruited; laboratory confirmed cases, and coughing household contacts. The latter group is a proxy for pertussis which is not laboratory confirmed.

There was a marked difference in the overall QALY loss between the two groups with 0.1 QALY for the confirmed cases and 0.04 QALY for the non-confirmed cases [16]. The health care costs were £55.55 for those confirmed and £25 for the coughing house hold contacts.

Vaccine efficacy

There are two licensed acellular pertussis-containing vaccines that can be used for maternal immunisation, Repevax™ and Boostrix/IPV™. Both contain low-dose diphtheria toxoid plus tetanus toxoid in combination with acellular pertussis and inactivated polio antigens but differ with respect to the number and amount of pertussis antigens each contains. Repevax™ was used for the maternal immunisation programme until July 2014 and its effectiveness estimated as 91% [1] but its efficacy as a booster dose in adults has not been evaluated. Boostrix/IPV has not been evaluated in a maternal programme but has demonstrated efficacy against laboratory-confirmed pertussis in a randomised controlled trial in adolescents (89%, 95% CI: 19%-99%) [17]. For the purposes of this

evaluation it was therefore assumed that both booster vaccines are suitable candidates for use in a maternal programme and that the protection afforded to mother and infant by each is similar.

Cost effectiveness analysis

It is common practice in cost-effectiveness analysis to evaluate a supplementary strategy relative to the existing practice as baseline. Therefore the existing vaccination programme against pertussis was not re-evaluated. The analysis was performed from a health care payer's perspective, in line with the recommendations of the National Institute of Clinical Excellence (NICE). The impact of the discount rate was investigated in 2 scenarios; discounting both QALYs and costs with 3.5%, and discounting both with 1.5%. To reflect the incorporated disease burden within the cost effectiveness analysis the discounting was applied to the estimated number of future cases. The programme was evaluated with 4 different time horizons: 5 years, 10 years, 30 years, 200 years. The assumed vaccine price was £10 or £15 plus £7.50 administration costs per dose. The uncertainty in the cost-effectiveness results were based on 1000 samples using Latin hyper cube sampling from the assigned distributions. All analysis was performed in R 2.14.1 [18] and an overview of all the used assumptions are given in table 1.

For the probabilistic sensitivity analysis, distributions were assigned. To derive an average value a normal distribution was used defined by the mean and standard deviation (SD) of 1000 bootstrap samples of the original data (so to obtain an average of the mean); to derive a percentage a beta distributions was assigned so to constrain the values between 0 and 1, again based on the mean and SD of 1000 bootstrap samples of the mean. For costs inputs triangular distributions were used, with the published maximum and minimum [11] as the upper and lower quartile

Results

In figure 1 the incidence in infants and women aged 20-44 is shown. As can be seen the disease between the two age groups follows a similar time course, underpinning the assumption that disease acquisition among mothers and infants is closely related, but with a time lag likely due to the later recognition and confirmation of adult compared with infant cases.

The sine wave used in the model is based on the outbreak in 2012 (figure 2). In table 2 the disease burden using this model and the observed number of cases in 2012 are compared and shown to be similar, with 590 observed and 554 modelled infant cases and 15 vs 17 deaths. It should be noted that in October 2012 maternal vaccination was introduced, reducing the number of infant deaths. After introduction of the maternal programme, the peak months had an incidence of 28 per 100,000 population months in infants under 3 months, and troughs of 3.5 per 100,000 population months.

In the base case incidence scenario, among a vaccinated birth cohort (60% coverage), there would be an expected 1800-2000 hospitalisations (3.5% and 1.5% discounting respectively) over the first 10 years after introduction, which would include 55-60 deaths. Around 20,500 cases (3.5% discounting) would l be prevented among mothers, of which around 1800 would be severe. However, the 95% confidence interval around the 20,500 cases is 4,500 to 24,500, reflecting the wide CIs around the vaccine efficacy estimate in adults (Table 3). The annual costs of the programme are £7.3 million assuming a price of £10 per dose and £9.4 million assuming £15 per dose. See table 3 for a detailed breakdown of the gained costs and QALYs due to the maternal vaccination programme and the related incremental cost effectiveness ratio (ICER). The cost-effectiveness of the programme is driven by the prevented mortality among infants, as vaccinating only for the benefit of adults is not cost-effective.

Projecting the 2010-2012 incidence into the future, with a peak every 4 years, the costs per QALY gained vary considerably depending on the discount rate, time horizon and vaccine price. Figure 3

shows the fluctuation in the price per dose in which 50% of the iterations are cost-effective (under the £20,000 threshold) over time in the base-case model. Table 4 shows the percentage of iterations in which the ICER is below a £20,000 or £30,000 cost per QALY threshold for different scenarios. When using discounting as recommended by NICE (3.5% for both costs and disease burden) in only one scenario are more than 50% of the iterations below the £30,000 threshold (5 year time horizon). Using discounting of 1.5% for costs and 1.5% for disease burden, all investigated scenarios have around 90% of the iteration below £30,000 (in case of a price of £15 this is at least 50%).

The findings above are very sensitive to the modelled incidence. When the incidence in both the peak and troughs is increased by 35%, at least 88% of the iterations achieve ICERs below £30,000 (3.5%/3.5% discounting and a vaccine price of £10) in all investigated time horizons, see table 5. Assuming that the incidence remains at peak level in 2012, then the programme would be highly cost effective, with an ICER of £16,865 (£12,209-£25,976; price of £10 and 3.5%/3.5% discounting).

The timing of introduction of the programme influences the overall cost-effectiveness, especially for short time horizons with a higher discounting scenario, as is shown in figure 4.

Discussion

Our cost effectiveness analysis shows that maternal pertussis immunisation would be highly cost effective if the peak incidence of infant disease at the time the programme was introduced, continues. However, our estimates were highly dependent on the future incidence of pertussis in infants under 3 months of age. This is necessarily difficult to predict given the uncertainties around the reasons for the resurgence and the transmission dynamics of pertussis. Although there has been a cyclical pattern in the past, it is not as steady and clear as simulated in our model. Moreover there may be more variation in the peaks and troughs in the future, as well as in the inter-epidemic period, which up to now in the UK has remained unchanged at 3 to 4 years since the start of vaccination in the 1950s. Although the sine wave fitted the 2012 outbreak well, when using it for projecting temporal patterns in future incidence, there is necessarily considerable uncertainty about the magnitude of future peaks and troughs especially for time horizons extending many decades into the future. For shorter time horizons, the timing of the peaks in relation to the start of the programme has a major influence on cost effectiveness due to the effect of discounting.

During periods of low incidence there is less direct benefit for the infant, but during periods with high incidence the benefit is considerably greater. The assumptions about future incidence in our model are therefore critical in determining cost-effectiveness. In the decade before the 2012 resurgence pertussis incidence was at an all-time low in England. However there are reasons to believe that there will be a sustained elevated incidence in infants and other age groups in the future, with peaks similar to, or larger than, observed in 2012. If the resurgence seen in the UK and some other countries is associated with the shorter duration of protection of acellular vaccines then there will be more susceptible individuals in the population than in the period when whole cell vaccine was used which is likely to result in an elevated endemic incidence. There is evidence for this from the US which introduced acellular vaccines in 1997; a resurgence was first seen around 2005 and an elevated endemic incidence has continued since then [19]. In England in 2014, which was a

trough year, there was a higher than expected number of laboratory confirmed cases and deaths among infants under 3 months of age compared with the pre-resurgence trough year of 2010, having taken into account the impact of a continuing effective maternal immunisation programme (PHE). This suggests that the elevated incidence first observed in 2012 is likely to continue and be reflected in both trough and peak years.

The vaccine prevents a greater number of infections in the mother than the infant. This is because the infant is only protected for 3 months compared to almost 4 years of the mother. However the disease burden is significantly greater in young infants who are at risk of death and may require invasive procedures such as ventilatory support. Therefore the prevention of pertussis in infants contributes more to the overall cost-effectiveness than prevention in the mothers. Another limiting factor related to this, the number of death due to pertussis in infants is likely to be higher due to under ascertainment leading to an even greater relative burden among infants. In adults the impact of pertussis is on the quality of life which is adversely affected by the prolonged, severe cough as it disrupts sleep and interferes with normal daily activities. The QALY loss in adults with confirmed pertussis and in their coughing household contacts was estimated during the 2012 resurgence [16]. However, estimating the overall burden of pertussis in the population remains difficult. The confirmed cases for whom we have information probably represent the most severe end of the illness spectrum and therefore the distribution of patients with severe and less severe symptoms remains speculative.

Due to the high efficacy of the maternal vaccination programme and the relatively high uptake of the vaccine, other approaches to prevent the disease burden in infants (in the first two months of life) have not been considered in this cost-effectiveness analysis. These include neonatal vaccination, where the new born receives a dose just after birth, and a cocooning strategy where the mother (and other household members) receives the vaccine after birth. A neonatal dose will not confer the 91% protection estimated for maternal immunisation as efficacy of single dose at around

2 months of age is only about 50% [6]. Moreover there is an expected delay in vaccine response leaving the infant unprotected in the first two weeks of life. Therefore such a programme will be considerably less effective and therefore less cost-effective compared to a maternal programme. The cocooning strategy aims to protect the infant from exposure by proactively vaccinating likely contacts of the neonate. However, this requires the vaccination of more individuals than just the mother, and is reliant on the efficacy of the acellular pertussis vaccine against transmission of infection.

Due to the periods of low incidence, the cost effectiveness of the maternal programme could be improved by switching it off at times of low incidence and on again when incidence increases. However this approach would be programmatically challenging as it would require a clear and timely trigger for the "on switch". While this is done with the use of antivirals for influenza, which are recommended when consultations for influenza-like-illness achieve a pre-defined rate, this would be more difficult for pertussis because of the delay between onset, disease recognition, laboratory confirmation and reporting. Furthermore for the infant to achieve the maximum benefit the optimal timing of vaccination is before the period when antibodies are actively transferred across the placenta, which is believed to commence around week 32 [20]. Therefore to make sure infants are protected at the high incidence period the programme needs to be initiated at least two months before the peak, to allow enough time for seroconversion in the mother and transfer of the antibodies. This would require a sensitive and reliable incidence-based trigger – one that preferably does not rely on an increase in infant deaths which was the trigger for the 2012 maternal immunisation programme. Also, by switching the programme off because of cost-effectiveness reasons society will have to accept that potentially preventable infant deaths will occur in the low incidence period.

The cost effectiveness of the maternal programme was assessed as a supplement to the existing 4 dose paediatric programme. With the high coverage of the existing programme in England

the incidence of disease in infants too young to be vaccinated has already been substantially reduced from the pre-vaccine era. As a result, the cost effectiveness of the maternal programme under the baseline incidence scenario was not favourable. This is despite the residual high morbidity and mortality in infants even before the recent resurgence when the annual admission rate in infants under 3 months was still over 1 per 1000 with 7 pertussis deaths per million maternities (14, 18). The main objective of existing pertussis programmes is to reduce infant morbidity and mortality [9]. Had maternal vaccination been an option when national vaccination was first introduced in the 1950s it may well have been the initial strategy chosen to achieve immediate infant protection with mass child hood vaccination considered later. However when introduced as an adjunct to an existing mature paediatric vaccination programme it may not appear cost effective. Our results are therefore highly context dependent and reflect the historical evolution of the UK programme. In other settings where vaccine coverage and disease control is poorer, the incremental benefit of maternal pertussis vaccination will be greater. Its administration would be facilitated in those countries already offering tetanus vaccine in pregnancy by the development of a low priced combined acellular pertussis/tetanus vaccine.

In addition to cost-effectiveness other factors merit consideration. First, is the absolute budget impact of the programme which will be relatively inexpensive as it will cost below £10 million per year. Second, is the guaranteed protection the programme provides, compared with the uncertainties of relying on herd immunity. It therefore provides reassurance that whatever happens to the transmission of disease in the future we have an intervention in place that can protect vulnerable infants. Third, are the wider benefits that will accrue from that programme that have not been included in the current cost-effectiveness analysis. Under the NICE guidelines, any QALY loss to care givers is not included in a cost-effectiveness analysis. Nevertheless prevention of death of a young infant prevents grief in the parents and their direct social network. Fourth, the direct protection of the mother, which will last for some years, might prevent transmission within the household on later occasions. A recent household contact study in the Netherlands showed that

mothers played a key role in transmission of pertussis to other household members as well as her infant [8].

Other countries have used alternative strategies to control the transmission of pertussis such as a booster dose in adolescence. However the direct contact between adolescents and young infants is low [21], hence the impact of this programme relies on the vaccine having an impact on disease transmission and the importance of adolescents in driving the infection among people who do have contact with infants. Pertussis incidence in infants under one year of age has continued to rise despite the introduction of the adolescent booster in the US, though coverage has not been high [19]. Also vaccinating adolescents might increase the average age of infection resulting in more susceptible young mothers.

In conclusion, while maternal vaccination is a highly effective intervention for preventing deaths and severe pertussis illness among young infants, its ICER as judged by standard NICE criteria may not be favourable if future incidence remains as observed in 2010-2012. However the maternal programme has a major benefit compared with the existing paediatric programme as it offers the opportunity to directly protect this highly vulnerable population, who previously could only be indirectly protected by herd immunity which has proven to be unreliable. Given the uncertainty about the ability of acellular vaccine to protect against transmission and maintain high levels of herd immunity, provision of passive protection to infants until they can develop their own active immunity through vaccination would seem prudent at least for the time being. Therefore it has been decided to keep the maternal vaccination in place in the United Kingdom for at least another 5 years, and to re-evaluate its cost-effectiveness in the light of the future epidemiology of pertussis [22].

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Conflict of interest

The authors do not have any conflict of interest to declare. All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributions

AJVH, HC, GA, NA and EM concpetualised the study. AJVH, in assistence of HC and NC, collected and structured all the input. AJVH performed all the modelling and programming. AJVH and EM drafted the first manuscript. All authors read and commented on the final draft.

Transparency

AJVH affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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1 **Tables**

2 Table 1 Overview of all the input parameters

Parameter	percentage/cost	Distribution	Source
Infants			
Outcome of hospitalisation			
Percentage patients no overnight stay	8.3% (SD 0.0088)	Beta	HES
Percentage patients requiring PICU	9.7% (SD 0.0090)	Beta	HES
Percentage patients PICU with ECMO	8.3% (SD 0.0242)	Beta	PICAnet
Percentage patients PICU retrieved	6.0% (SD 0.0429)	Beta	PICAnet
Duration of stay not admitted to PICU	5.5 days (SD 0.172)	Normal	HES
Duration of stay PICU, no ECMO	6.0 days (SD 0.644)	Normal	PICAnet
Duration of stay PICU, ECMO	18.1 days (SD 4.097)	Normal	PICAnet
Costs hospitalisation			
Hospital visit without overnight stay	£422 (min £282-max £523)	Triangular	Reference costs 2012-2013 PA65A
Overnight stay hospital, no PICU	£758 (min £552- max £885)	Triangular	Reference costs 2012-2013 PA65B
Overnight stay PICU, no ECMO	£2110 (min £2004- max £2130)	Triangular	Reference costs 2012-2013

			XB04Z
Overnight stay PICU, ECMO	£4391 (min £3966 - max £4768)	Triangular	Reference costs 2012-2013 XB01Z
Costs retrieval PICU	£2799 (min £2350- max £3209)	Triangular	Reference costs 2012-2013 XB08Z
Mortality			
Proportion died	3.1% (1.75%-4.7%)	Binomial	Enhanced surveillance PHE
Utility and life years lost			
Mortality and morbidity in infants			
	Undiscounted	Discounted 1.5%	Discounted 3.5%
LY lost in case of death	80.6	46.7	27.3
QALY years lost in case of death	65.1	38.7	23.2
QALY loss in surviving infants	0.10070 (0.00482)	Normal	Assumption
Mothers			
Disease			
Percentage laboratory confirmed disease	8.8%	None	See text
Percentage non confirmed disease	20%	None	Assumption
Costs			

Mild disease	£25.63 (SD 4.81)	Normal	[16]
Confirmed disease	£55.55 (SD 1.59)	Normal	[16]
Utility			
Mild disease	0.03645 (0.00772)	Normal	[16]
Laboratory confirmed disease	0.09724 (0.0044)	Normal	[16]
Overall Costs and Utility per case			
Infant Costs	£5253 (95% CI:£4412-6126)		
Infant QALY loss discounted 1.5%	1.308 (95% CI: 0.776-1.913)		
Infant QALY loss discounted 3.5%	0.824 (95% CI: 0.504-1.188)		
Mother Costs	£10.01 (95% CI: £8.1-11.85)		
Mother QALY loss	0.018 (95% CI: 0.014-0.021)		
Vaccine parameters			
Efficacy Infants	91% (84%-95%)		[1]
Efficacy Mother	89% (19%-99)		[17]
Price	£10-£15		Assumption
Administration costs	£7.5		Assumption
Coverage neonatal and maternal immunisation	60%		Assumption
Births England	694241		[5]

Table 2 Outcomes of the model for a peak year (with a peak in month 8) compared to the observed number of cases and death in the year 2012.

	Observed in 2012	Model (peak year, with the peak in month 8)
Hospitalisation infants <3 months	590	557
Number of deaths	15*	17
Laboratory confirmed cases adult women aged 20-44	2063	2669
Non-confirmed pertussis cases among adult women aged 20-44	Not reported	6066

* Maternal vaccination was introduced on October 2012

Table 3 Prevented disease burden among vaccinated infants and mothers (coverage 60%) in a base case scenario with a time horizon of 10 years and 3.5% or 1.5% discounting.

	Discounting	Without vaccination	With vaccination	Increment
Cases infants	1.5%	1,995	180 (73 – 328)	1,815 (1,667-1,922)
	3.5%	1,809	163 (67 - 297)	1,646 (1,512-1,742)
Cases adults	1.5%	27,940	4,470 (0 – 22,706)	23,470 (5234-

				27,940)
	3.5%	24,509	3,921 (0 – 19,918)	20,588 (4,591-24,509)
Costs infants	1.5%	£10,483,088 (£8,805,632-£12,223,431)	£942,896 (£376,107-£1,749,613)	£9,540,192 (£7,855,902-£11,266,057)
	3.5%	£9,503,345 (£7,982,662-£11,081,037)	£854,774 (£340,956-£1,586,095)	£8,648,571 (£7,121,694-£10,213,137)
Costs adults	1.5%	£279,801 (£226,295-£330,976)	£44,647 (£0-£223,000)	£235,154 (£51,454-£321,890)
	3.5%	£245,444 (£198,507-£290,334)	£39,164 (£0-£195,616)	£206,279 (£45,136-£282,364)
QALY infants	1.5%	2609 (1548-3818)	236 (77-476)	2373 (1411-3501)
	3.5%	1490 (912-2149)	135 (44-271)	1356 (8230-1967)
QALY adults	1.5%	443 (356-533)	71 (0-365)	372 (84-505)
	3.5%	388 (310-468)	62 (0-320)	326 (73-443)

# Doses	1.5%	0	3,867,790	3,867,790
	3.5%	0	3,519,464	3,519,464
Programme costs (£10+£7.5)	1.5%	0	£67,687,790	-£67,687,790
	3.5%	0	£61,590,620	-£61,590,620
Programme costs (£15+£7.5)	1.5%	0	£87,025,279	-£87,025,279
	3.5%	0	£79,187,940	-£79,187,940
Vaccine price		£10+£7.5	£15+£7.5	
ICER only infants	3.5% / 3.5%	£39,464 (£26,895-£64,856)	£52,589 (£35,871-£85,951)	
	1.5%/1.5%	£24,783 (£16,554-£41,710)	£33,036 (£22,207-£55,401)	
ICER only adults	3.5% / 3.5%	£173267 (£138,512-£8,730)	£222,956 (£178,264£1,079,829)	
	1.5%/1.5%	£167,011 (£133,507-£809,498)	£214,912 (£171,828-£1,040,960)	
ICER overall	3.5% / 3.5%	£31,605 (£22,834-£48,343)	£42,070 (£30,495-£64,282)	
	1.5%/1.5%	£21,263 (£14,939-£33,765)	£28,340 (£20,045-£44,938)	

1

Table 4 Price per dose with 50% and 90% below the threshold, and the percentage of iterations (of a total of 1000) with an ICER under the threshold of £20,000 or £30,000 using 4 different time horizons (5 years, 10 years, 30 years and 200 years), different vaccine prices (£10 and £15 + £7.5 administration costs) and discounting scenarios (3.5% costs/3.5% QALYs and 1.5% Costs /1.5% QALYs).

3.5% Costs/3.5% QALYS	5 year horizon		10 year horizon		30 year horizon		200 year horizon	
Threshold	<£20,000	<£30,000	<£20,000	<£30,000	<£20,000	<£30,000	<£20,000	<£30,000
3.5% Costs/3.5% QALYS								
£10+£7.5	0%	48%	0%	40%	0%	29%	0%	25%
£15+£7.5	0%	4%	0%	2%	0%	1%	0%	1%
1.5% Costs/1.5% QALYS								
£10+£7.5	46%	95%	38%	93%	26%	90%	23%	88%
£15+£7.5	4%	69%	2%	61%	1%	50%	1%	46%

Table 5 Price per dose with 50% and 90% below the threshold and the percentage of iterations (of a total of 1000) with an ICER below the threshold of £20,000 or £30,000 using 4 different time horizons (5 years, 10 years, 30 years and 200 years), different vaccine prices (£10 and £15 + £7.5 administration costs) and scenarios with a 35% higher disease incidence. Only the discounting of 3.5% costs/3.5% QALYs is shown, as this scenario was the least cost-effective.

3.5% Costs/3.5 % QALYS		5 year horizon		10 year horizon		30 year horizon		200 year horizon	
35% Higher peak/higher low	Threshold	<£20,000	<£30,000	<£20,000	<£30,000	<£20,000	<£30,000	<£20,000	<£30,000
	£10+£7.5	39%	95%	30%	92%	20%	89%	17%	88%
	£15+£7.5	2%	60%	1%	51%	0%	40%	0%	36%

Figures

Figure 1 Monthly incidence of hospitalised pertussis among infants (left axis) and laboratory confirmed cases among women aged 20-44 years (right axis).

Figure 2 Comparison of the disease incidence model with peaks every 4 years as observed in 2012.

Figure 3. The fluctuation of the cost-effective price per dose in the base-case scenario. In high incidence years the price is over £10 (3.5%/3.5% discounting), however in the low incidence years the price per dose is below £0, which means that the maximum cost per dose goes below £7.5 (the administration cost).

Figure 4 The effect of an expanding time horizon on the price. Shown is the price at which 50% of the scenarios is deemed cost-effective under a threshold of £20,000 with an expanding time horizon under the two discounting scenarios. The value of 2 months, uses a time horizon of 2 months, 3

month/ 3 month etc. The profile of the first few years is highly dependent on where you start in the epidemic cycle.

Figure

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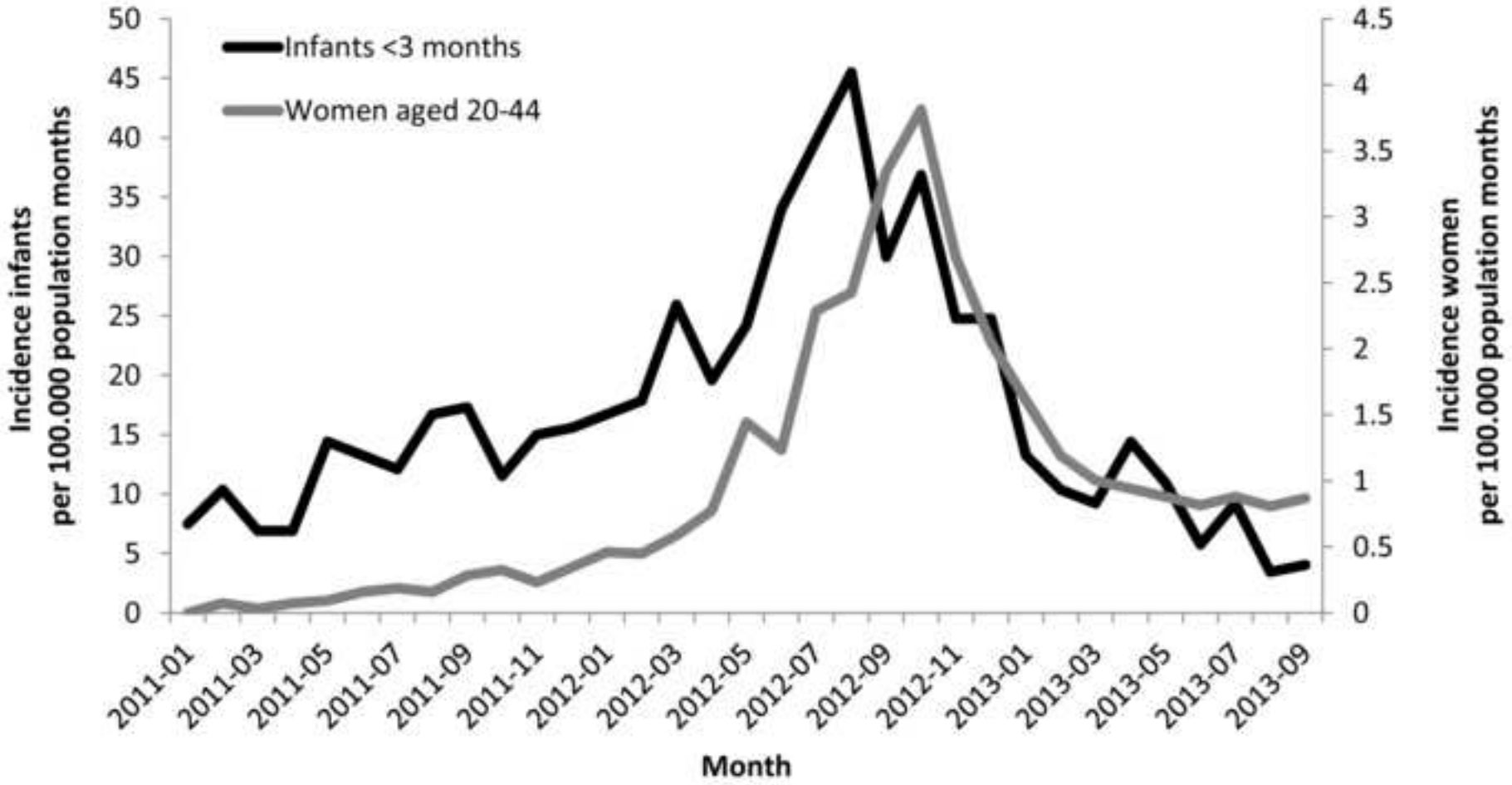

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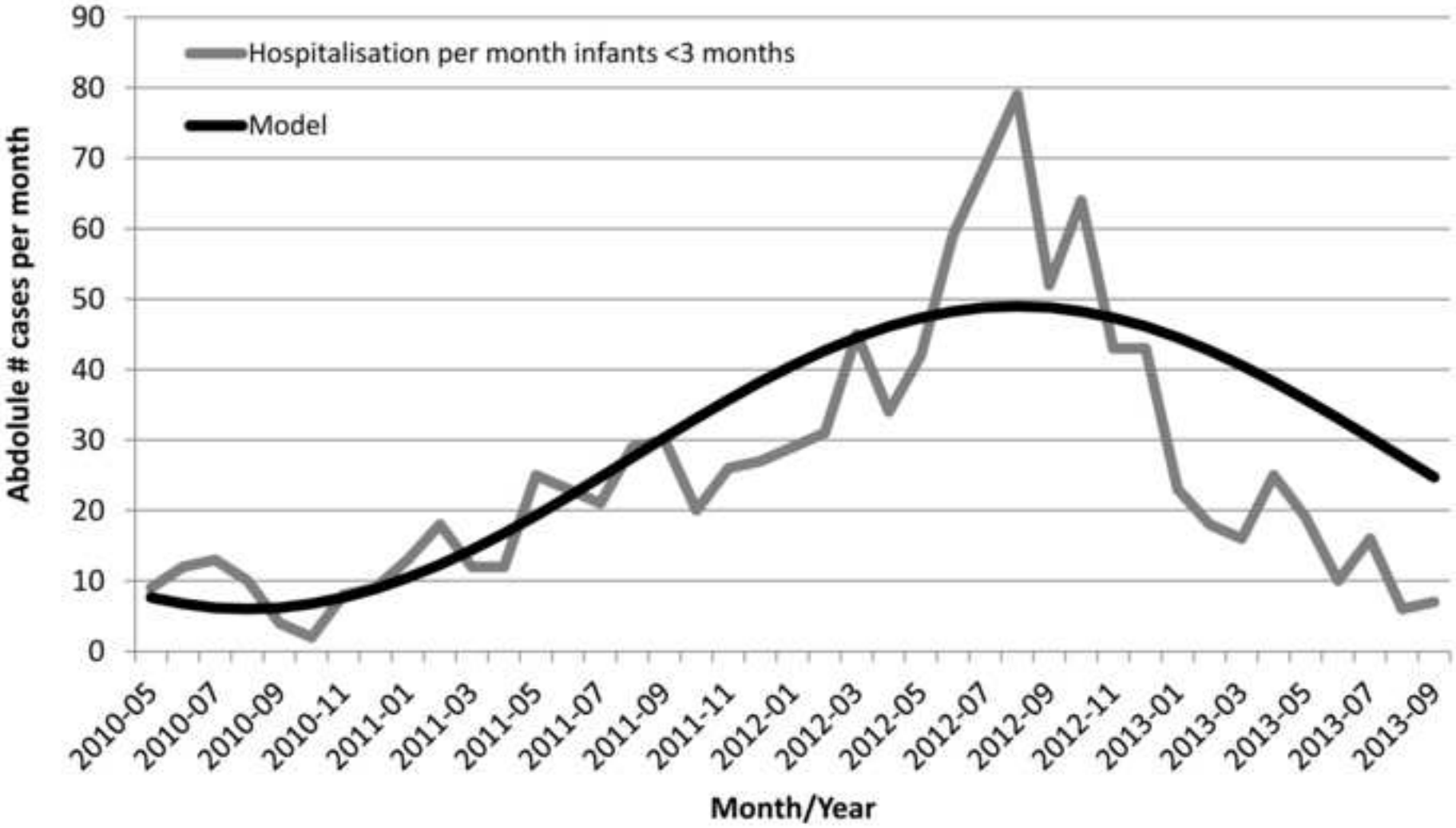

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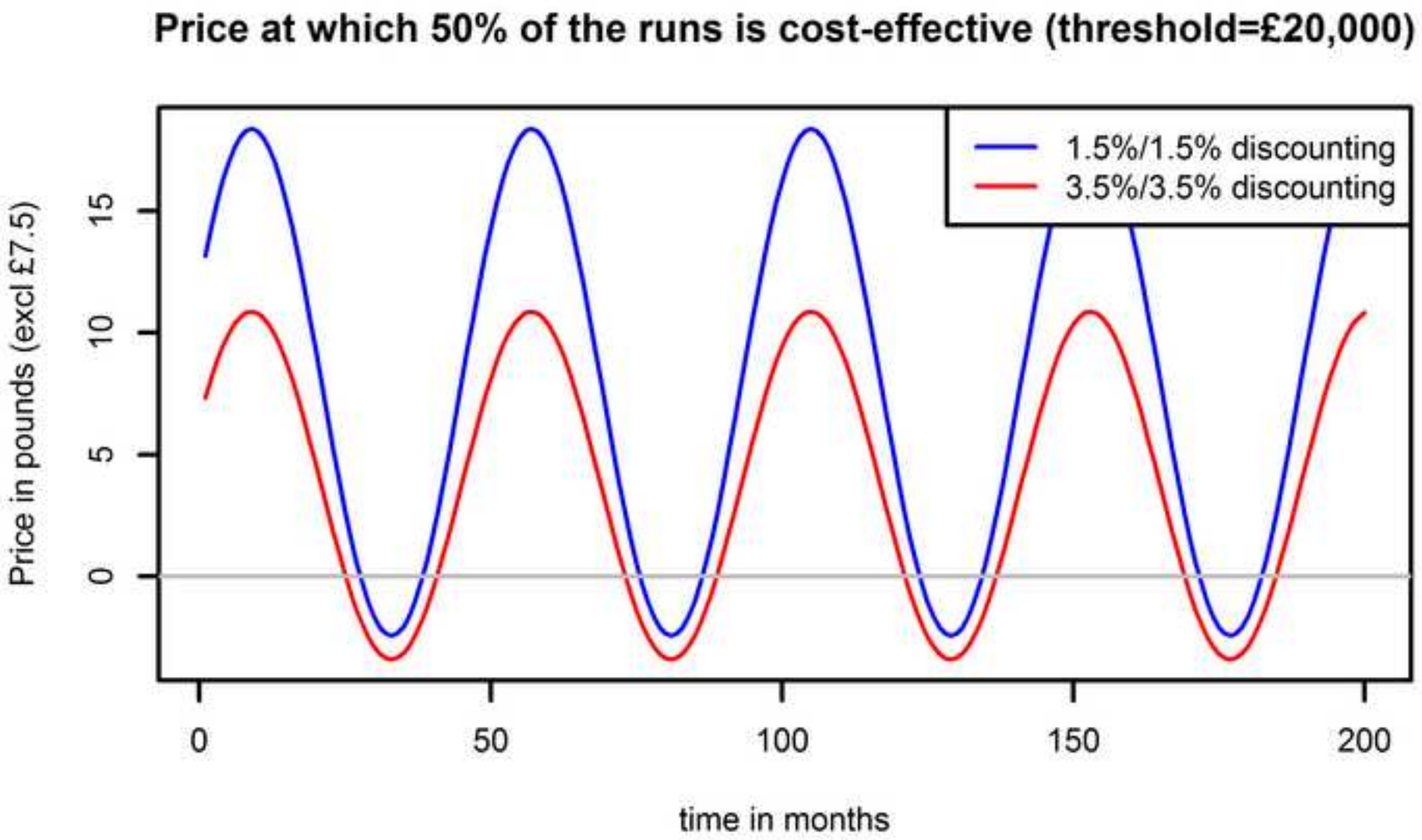

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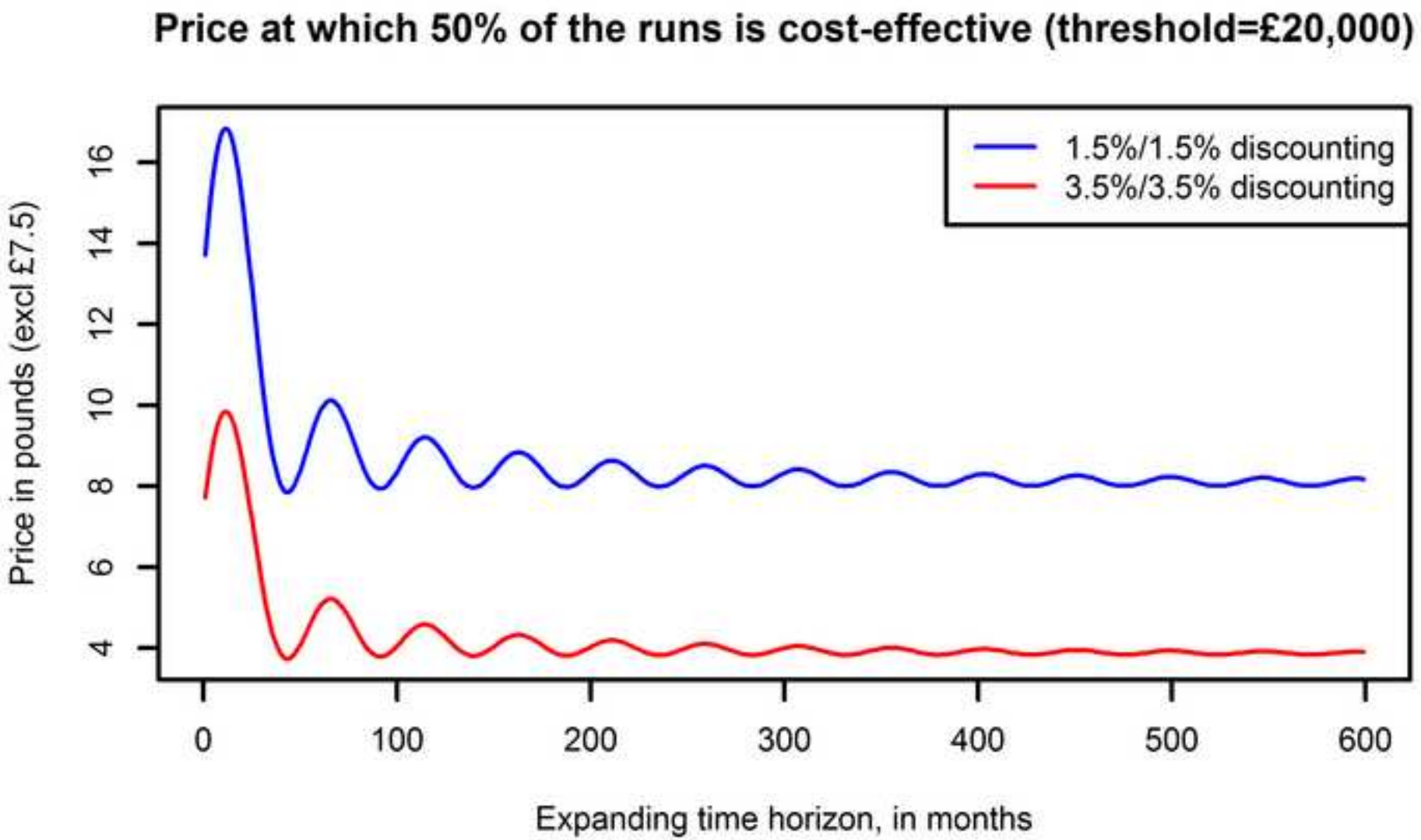

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