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How to prevent vaccines falling victim to their own success: Inter-temporal dependency of incidence levels on indirect effects in economic re-evaluations

Running Head:

Herd protection in incremental re-evaluations

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Vaccination, externality, Herd Immunity, Cost-Effectiveness Analysis, decision making

Abstract

Objectives: Incremental cost-effectiveness analyses may inform the optimal choice of healthcare interventions. For many vaccines, however, benefits fluctuate with incidence levels over time. Re-evaluating a vaccine after it successfully decreased incidences may eventually cause a disease resurgence if switching to a vaccine with lower indirect benefits. Decisions may successively alternate between vaccines alongside repeated rises and falls in incidence, and when indirect effects from historic use are ignored. Our suggested proposal aims to prevent sub-optimal decision making.

Methods: We used a conceptual model of demand to illustrate alternating decisions between vaccines due to time-varying levels of indirect effects. Similar to the concept of subsidies, we propose internalising the indirect effects achievable with vaccines. In a case study over 60 years, we simulated a hypothetical 10-year re-evaluation of two oncogenic human papillomavirus vaccines, of which only one protects additionally against anogenital warts.

Results: Our case study showed that the vaccine with additional warts protection is initially valued higher than the vaccine without additional warts protection. After ten years this differential decreases due to declines in warts incidence, which supports switching to the non-warts vaccine that causes a warts resurgence eventually. Instead, pricing the indirect effects separately supports continuing with the warts vaccine.

Conclusions: Ignoring how the observed incidences depend on the indirect effects achieved with a particular vaccine may lead to repeated changes in vaccines at successive re-evaluations, with unintended resurgences, economic inefficiencies, and eroding vaccine confidence. We propose internalising indirect effects to prevent vaccines falling victim to their own success.

Concise description of article (no more than 25 words):

Changing the vaccine used in existing vaccination programmes may reduce indirect effects and cause disease resurgences. We propose internalising indirect effects explicitly in incremental (re-)evaluations.

Words: 25

2-3 Highlights (1. What is already known about the topic? 2. What does the paper add to existing knowledge? 3. What insights does the paper provide for informing health care-related decision making?)

1. The importance of the indirect herd effects of vaccines is widely recognised and frequently included when evaluating the long-term impact of introducing new vaccination programmes over sufficiently long timeframes or until steady state is reached, but when re-evaluating vaccines incrementally some time after vaccination introduction the indirect herd effects achieved in the past are infrequently considered explicitly, or assumed to have been realised or even persist with alternative vaccines.

2. This paper illustrates the issue of repeated changes between vaccines with different indirect effects in subsequent incremental (re-)evaluations when failing to account for the indirect herd effects achieved in the past with the initially introduced vaccine. These indirect herd effect levels are required to maintain the observed lower incidence levels, which may make the initially introduced vaccine look less cost-effective over time. Switching between vaccines with similar direct effects but different indirect effects based on the incremental cost-effectiveness at the time of the re-evaluation may cause disease resurgences, economic inefficiencies, welfare losses, erosion of vaccine confidence, and lower vaccine uptake.

3. Our paper aimed to raise awareness for the potential to make sub-optimal decisions based on economic (re-)evaluations of vaccines when ignoring indirect effects achieved in the past since vaccination introduction. Furthermore, although indirect effects could be accounted for qualitatively during appraisals and price negotiations, we also propose a solution of explicitly internalising indirect herd effects of vaccines in each (re-)evaluation, similar to the economic concept of subsidies. For instance, indirect effects could be priced at constant rates based on the entire herd protection achieved since vaccine introduction and still expected to be achieved with a vaccine over a sufficiently long time period.

Introduction

Cost-effectiveness analysis is used in many countries to inform decisions about changes to national healthcare programmes, such as the introduction of a new intervention or expansion of the population eligible to receive an existing intervention.(1-3) It may also be used to inform analyses of whether adopting an intervention has been worthwhile,(4-6) and to inform prices that reflect the intervention's economic value.(7-9) Furthermore, several interventions may become available at different times and with mutually exclusive uses but different clinically relevant features, with more information about efficacy and duration of protection possibly becoming available gradually over time. For instance, several vaccines are available against human papillomavirus (HPV), which prevent infections leading to most cervical cancer cases but differ in terms of price, valency, immunogenicity, and disease endpoints in their indication. The optimal approach should be to maximise the net value of an intervention compared to its comparators, i.e. the value of the health and economic benefits of disease prevented and alleviated minus the opportunity cost of using the intervention.(10-13) However, investment decisions based on economic evaluations may need to be reconsidered, accounting for any changes in price, disease epidemiology and characteristics of the intervention if different vaccines become available, more information had been gathered, or to inform competitive bidding to curb expenditures.

Despite the health and economic benefits of evaluating and choosing interventions based on their incremental net value, typically the same methods used to inform the initial decision to introduce an intervention are also used to inform subsequent re-evaluations of the introduced intervention after some time.(4) In particular, the cost-effectiveness of any change is evaluated incrementally, i.e. in terms of the difference in costs and health outcomes of the changed situation compared to the counterfactual.(4) When a change in interventions is evaluated, the counterfactual is keeping the status quo indefinitely. However, an existing intervention may already have been used for several years, and so an incremental analysis normally dictates that replacing it with a new intervention should be compared to the counterfactual of continuing with the current intervention. The new intervention should then be used instead only if the additional benefit of the intervention are worth the additional price of the new intervention compared to the current

one, even if the new intervention is overall cost-effective compared to no intervention.(14) The same principles hold if the decision to continue with a vaccination programme is re-evaluated decrementally (e.g. compared against fewer vaccine doses, or no-vaccination).(15, 16)

These methods work reasonably well for most healthcare technologies against non-communicable diseases with little to no impact on others (i.e., third parties).(4, 14) They also work for infectious diseases where vaccination, infection, and disease occur in quick succession or without impact on the complex dynamics of infection epidemiology.(17) However, for many vaccines, each infection prevented has the potential to reduce transmission to others – the so called "indirect effect", "herd protection",(18) or "positive externality" of vaccination.(19) This indirect protection is crucial to immunisation programmes in helping to protect not only the vaccinated individuals but also unvaccinated and vulnerable populations.(20) Ignoring them may result in decisions that lead to economic inefficiency and welfare loss as the social benefits are higher than the direct (private) benefits.(21, 22) Furthermore, the risk of acquiring an infectious disease can vary over the course of a vaccination programme, depending on the changing immunological profile of the population, as well as the success of the vaccination programme in reducing cases circulating, and other epidemic changes.

Specialist techniques such as transmission-dynamic models are able to include the indirect effects of vaccinations.(20, 23, 24) However, a vaccine may wrongfully appear less cost-effective in incremental re-evaluations some time after having introduced vaccination when incidence levels have been successfully lowered by the vaccine – when ignoring the indirect effects achieved and required to maintain the observed lower incidence levels. If the decision was then made when uptake is high and incidence low to switch to a different vaccine with lower levels of indirect effects, a rebound effect of cases may occur depending on the protection conferred by the new vaccine, and lead to alternating decisions between vaccines in subsequent re-evaluations with rising and falling incidence levels (i.e., once enough susceptibles have built up again the herd protection would justify switching back to the first vaccine, and so on).(25) Such start-stop or switching decisions are economically inefficient and undesirable given that vaccination uptake is easily disrupted,(26-28) with potential knock-on effects on public confidence in vaccines, (inter-generational) equity in vaccine access, manufacturer pricing

strategies, and the long-term benefits of vaccination. Note that these issues may not arise for different vaccine products with similar total benefits, or in case the alternative vaccine can offset lower indirect effects with higher direct effects (including higher coverage).

This paper aims to highlight the issue of positive but temporary indirect effects induced by vaccines over time, and to describe a method for addressing this in economic re-evaluations. It first presents some background to illustrate these issues and our proposal from the healthcare provider perspective, before using a hypothetical case study of re-evaluating two HPV vaccines.

Background

Part 1: Conceptual illustration of changing incidence levels over time due to alternating decisions.

Figure 1 shows disease incidence changing as a result of alternating decisions between two vaccines. We considered two hypothetical vaccines labelled "A" and "B", and only one of the two vaccines can be used at any given time (i.e., A and B are mutually exclusive). We assume that vaccine A is preferred over vaccine B due to e.g. higher efficacy and/or herd protection. Vaccine A is introduced at t=0 as it is found to be cost-effective at that time; it reduces overall disease incidence due to direct and indirect protection (cf. solid black line over 0-T_3). At T_3 the cost-effectiveness of the vaccine is re-evaluated; vaccine B or indeed "no vaccine" appear to be reasonable alternatives given the low disease incidence (Figure 1A). In reality, however, this risks ignoring the transient nature of the residual indirect effects of vaccine A as the observed incidence would have been higher had the alternative vaccine B (or no vaccine) been used since t=0. Therefore, the re-evaluation at T_3 can lead to one of three outcomes (Figure 1B):

(i) Continue using vaccine A; resulting in a disease incidence at a continued low level as indicated by the lowest, horizontal dashed line.

(ii) Switch to vaccine B; resulting in a disease incidence that rises to a new equilibrium level (due to the e.g. lower efficacy and/or herd protection) as indicated by the middle horizontal dashed line.

(iii) Stop using either vaccine; resulting in a disease incidence that returns to initial levels of the highest horizontal dashed line (with how quickly this return happens depending on disease dynamics driving how fast population immunity is lost).

Further re-evaluations may occur at T_4, T_5, T_6, T…, where the decision may change each time to switch back to the other vaccine and/or no vaccination and thus result in periodic waves of disease resurgences (Figure 1B).

[Figure-1-here]

Note how the curve of "no vaccine" in T_3-T_6 is shown symmetrical to 0-T_3, and the alternating curve between vaccines B and A over T_3-T_6 is (largely) symmetrical to the curve at T_2-T_3; conceptually, the issue can indeed be reduced to moving on the curve depicted between 0-T_3 in a bi-directional dimension, as is commonly done in economics (and also in the figures used in the next sections). Also, the illustrative figure cannot show how changing incidence levels translate to changing decisions in terms of cost-effectiveness (or net benefits) given that these changes may not be proportional; cf. the potentially larger quality-adjusted life year (QALY) loss prevented in infants vs. the elderly.

Part 2: Economic model of demand from a healthcare provider perspective that alternates between vaccines over time due to positive but time-varying externalities.

To illustrate the inter-temporal impact of positive but temporary externalities, we will consider an economic model of supply and demand from the healthcare provider perspective that builds on earlier studies.(7, 8, 29) Note that it is well-known that this conceptual model does not reflect reality due to its simplifying assumptions, particularly for goods such as vaccines which have high sunk costs (for research and development), externalities, information asymmetries and other important deviations a perfectly competitive market. However, in the interest of generalisability, it provides useful insights for the illustration of ideas. Here, we consider two mutually-exclusive vaccines A and B again, and we assume that the value of the direct net benefits of vaccine A (i.e., excluding indirect herd effects) is initially higher but gradually declining until the value of the direct net benefits is higher with vaccine B so as to illustrate the issue of switching vaccines, which may be e.g. due to a higher efficacy of A but fewer cases left to prevent with declining incidence (similar to T_3-T_6 in Figure 1). For simplicity, the value of the direct net benefits of vaccine B remain constant, and only vaccine A offers additional but diminishing indirect effects (i.e., vaccine B offers no indirect effects for simplicity; otherwise the values of the indirect net benefits of vaccine A and B would need to be offset, too). The healthcare provider informs the initial pricing negotiations for both vaccines against a pre-set cost-effectiveness threshold (i.e., the values represent where the vaccine prices equal the threshold of e.g. £20,000 per QALY gained in England and Wales),(7, 8) and the demand curve is equal to the highest net benefit

obtained from either vaccine. Lastly, the supply curve is assumed with the minimal price at which the supplier will generate a return on investment, i.e. equal to the marginal costs of production in the case of no sunk costs, and which are assumed to be constant and approximating marginal social costs.(30) The supply curve is only required to illustrate the rare situation of the marginal costs of vaccine production exceeding the net value to healthcare providers; a more thorough exploration of the shape of the supply curve of drugs under similar conditions as described here has been reported elsewhere.(29)

Figure 2 illustrates these assumptions and the potential pricing of the two vaccines A and B over three points in time (depicted in equidistance for simplicity again). The healthcare provider demand for vaccines is shown as dashed line. Then, at 0-T_1, vaccine A should be procured over vaccine B given the higher direct net benefits (P_2-0 vs P_1-0, respectively) and the additional indirect effects with only vaccine A (P_4-P_2). At T_1-T_2, the healthcare provider would continue with vaccine A given its lower valued but continued indirect net benefits (P_5-P_1). At T_2-T_3, the direct net benefits of vaccine B are expected to be higher than the direct and indirect net benefits of vaccine A (difference of P_1-P_3 and P_1-P_6, respectively), and the provider would consider switching to vaccine B – when ignoring the indirect effects achieved over 0-T_2.

Notably, the positive indirect effects always justify higher prices than the direct effects alone, which conversely translates to lower incremental cost-effectiveness ratios (ICERs) at the price of the direct effects alone.(23) With marginal costs of P_1 for both vaccines, however, vaccine A becomes unfeasible for the manufacturer and society at T_2-T_3 (welfare reducing),(22) even when considering the indirect effects at T_2-T_3 and the fact that vaccine B induces no indirect effects itself here.

Next, after having switched and used vaccine B for some time and with the build-up of enough susceptible individuals, the horizontal time axis can be interpreted in a bidirectional dimension; i.e., the direct and indirect net benefit of vaccine A may rise again (as at T_2-T_1), justifying a switch back to A if the vaccines were re-evaluated once more (and when considering net benefits from indirect effects; otherwise the switch back would occur when re-evaluating at higher levels as seen at T_1-0).

[Figure-2-here]

Part 3: Proposal addressing the intertemporal dependency of incidence levels on vaccine demand and herd protection.

Given that externalities qualify for being internalised in prices (cf. Supplementary Material, Supplementary Figure 1), we propose to account for the inter-temporal changes in vaccine demand, herd protection and infection levels by pricing the indirect effects separately from direct effects. Thereby, the pricing should always consider the entire herd protection achieved and still achievable with a vaccine, while allowing the price of the direct effects to change with incidence. Essentially, the value of the indirect benefits is spread out evenly over time, possibly updated with additional information at each re-evaluation. The intended mechanism of this is to pay less for high levels of indirect net benefits observed at any one point in time given the expected indirect effects achievable over the entire timeframe, but also to pay more for lower levels of indirect effects observed at any one point in time given the herd protection achievable with a vaccine over the entire timeframe. Furthermore, the herd protection achievable over the entire time horizon from introducing a vaccine needs to be re-considered as the indirect effects achieved up until the time of re-evaluation may over- or under-estimate their value in future (depending on the shape of the indirect effects over time; see e.g. Boulier et al., 2007).(19)

This idea is illustrated in Figure 3, where the direct benefits of the vaccines are unchanged (cf. Figure 2), but the total indirect effects of vaccine A over 0-T_3 are internalised with P_4* (cf. dotted lines). Essentially, this aims to avoid higher prices by re-evaluating over the entire timeframe (0-T_3) instead of only when indirect effects are high (0-T_1), and to avoid lower prices by re-evaluating over the entire timeframe (0-T_3) instead of only when indirect effects are low (T_2-T_3), assuming they have been high before (0-T_2). Some of the value assigned to the indirect benefits at 0-T_1 is thus allocated to after T_1, which increases prices at T_1-T_3, leads to vaccine A staying in the market at T_2-T_3, and A being favoured across 0-T_3 given its indirect effects.

[Figure-3-here]

Methods

Case study of HPV vaccination

We used as a case study a published transmission dynamic model that was used to inform both the decision to introduce HPV vaccination in the UK in 2007,(31) as well as the subsequent switch from a bivalent to a quadrivalent vaccine following a competitive tender in 2010.(32) Here we used the model to estimate the impact of female HPV vaccination on the annual incidence of anogenital warts for illustration purposes only. While the scenarios we consider are hypothetical, the model has been previously fitted to HPV prevalence, warts incidence and economic parameters from the UK. It also illustrates the wide range of vaccines used for infectious diseases that may be characterised by a breadth of strains or types of pathogens covered, the number of doses required to achieve full efficacy, and the magnitude and duration of efficacy.

We consider the use of either a vaccine that protects against oncogenic HPV types (16 and 18) as well as HPV 6 and 11 that cause the majority of warts cases ("warts vaccine"), or a vaccine that purely protects against oncogenic HPV types and does not protect against HPV 6 or 11 ("non-warts vaccine"). In this example the two vaccines are assumed to be identical in all other aspects except for price. Vaccine-induced protection was assumed to wane exponentially in a range of scenarios between lifelong and ten years.(31) The two hypothetical vaccines approximate the actual difference between bivalent (Cervarix, GSK) and quadrivalent (Gardasil, Merck) HPV vaccines. However, for simplicity we do not consider here the other potential differences between Cervarix and Gardasil in terms of the adjuvant, the long-term immunogenicity reported in clinical trials, the licensure indications and the differing potential of each vaccine to show cross-protection against infection by non-vaccine types.(32)

We simulated the potential effect of two hypothetical competitive rounds of tendering to decide which vaccine to use in the national schedule: (i) the first round in 2007 to decide on the vaccine to use during 2007-2017, and (ii) the second round in 2017 to decide on the vaccine to use

thereafter. The starting point for the second analysis (the counterfactual) is the epidemiological situation at 2017, i.e. after 10 cohorts of girls had received the warts vaccination with a catch-up campaign in the first few years (of note, the UK actually introduced Cervarix in 2008 and switched to Gardasil in 2011). For simplicity, we assumed no further changes in the vaccine used after 2017. We then calculated the maximum price difference that would be needed in 2007 and 2017 in order for the warts vaccine to be preferred over the non-warts vaccine. This price difference was estimated based on the net present value of the benefits of warts prevention (in terms of costs saved and quality-adjusted life years gained) over a 50 year time horizon and using a threshold of £20,000 per QALY.(33, 34) The value of these benefits was discounted back to the year of the tender (2007 or 2017) at a rate of 3.5% per annum for both costs and health effects.(33, 34) We considered wart treatment costs per case of a mean of £113,(35) and mean QALY losses of 0.018.(36) All analyses were done in R software.

Results

Case study of HPV vaccination

Figure 4 shows the simulated effect that HPV vaccination could have on the annual incidence of anogenital warts, assuming that either the warts vaccine is the only vaccine used from 2007, or that the warts vaccine is used only until 2017 after which there is a switch to the non-warts vaccine (the spike in fully vaccinated girls is due to the campaign in the first few years). Of note, even after a switch to the non-warts vaccine is made the incidence of anogenital warts continues to decline for a few years due to the continued existence of cohorts of females that have been vaccinated with the warts vaccine. After decades, incidence of anogenital warts gradually returns to its pre-vaccination level, and the total benefits predicted in the analysis at 2007 and used to justify the higher price for warts vaccine at that stage, are not fully achieved.

The persistence of the indirect effect from the first ten years of vaccination disadvantages the warts vaccine in the second tender, since even if a switch was made to non-warts vaccine, some of the benefits of having used the warts vaccine in the past would still materialise. The

importance of these residual benefits is magnified by the use of discounting, which gives more weight to present benefits over those in the distant future.

[Figure-4-here]

Supplementary Table 1 shows the differences we would expect to see in selecting each vaccine either in the first or the second tender. The maximum additional price we would be willing to pay for the HPV warts vaccine for the indirect effects on warts prevention decreases by over 32% (from £116 to £77) between the first and second tender, and if a warts vaccine is consistently priced between £77-£116 more than a non-warts vaccine (e.g. with +£100), incremental cost-effectiveness analyses starting from the point of re-procurement would switch repeatedly between vaccines at successive re-evaluations when ignoring the indirect herd effects. If this reduction was completely due to indirect effects, i.e. the remaining additional price of £77 is entirely attributable to direct effects, the vaccine could continue to be priced up to £77+(£116-£77)=£116 with our proposal, and where the difference of £116-£77=£39 would thus be the estimated value of internalising the indirect benefits. However, one could also assume the entire price difference of warts prevention reflecting an indirect effect as the warts may not have been the prime focus for choosing HPV vaccines that target cervical cancer prevention. Then, if we account for the different timings of re-evaluation and assume proportional gains (the issues with this are discussed later), the vaccine would have generated a net value of warts prevention of £116 over the first 10 years and is still expected to generate a value of £77 over the next 40 years, leading to an adjusted additional vaccine price aiming to internalise the indirect benefits of £116*10/50+£77*40/50=£85. Note that HPV vaccination is a more complex situation as it uses multivalent vaccines that also help to control for another disease or strain at marginal extra costs. Furthermore, these simulated results are not meant to represent the actual HPV vaccination programme in the UK. However, the situation of switching HPV vaccines has some basis in reality, since the UK introduced Cervarix in 2008 and switched to Gardasil in 2011, both times following competitive tendering.(32)

Discussion

This study showed how initially cost-effective vaccinations may appear less cost-effective over time when ignoring the inter-temporal dependency of vaccine demand on the achieved herd protection and observed incidence levels. This happens when a successful vaccination programme reduces incidence and infection levels; an effect which may persist for years and decades even if the vaccine is no longer used (a form of path dependency, i.e. inherent to empirically observing one of many possible realisations that depend on decisions made in the past).(25, 37) In effect the vaccine may become a victim of its own success.

In line with the economic insight that externalities qualify for being internalised in prices,(22, 30) and certain situations being insufficiently captured by current practices,(38) we propose quantifying prices for the indirect effects of vaccines separately from direct effects. Transmission-dynamic models frequently include indirect effects already when evaluating the introduction of new vaccination programmes.(23, 24) In subsequent re-evaluations, however, the indirect effects achieved and still achievable with a vaccine need to be re-considered (i.e., the vaccine demand required to maintain the levels of herd protection achieved in the past and expected in future) as each cohort of patients experiences not just the vaccines that they receive but also the residual indirect effects from vaccination in the past. Prices may also be adjusted if expectations are not met or exceeded, and periodic re-evaluations may need to be conducted systematically to avoid gaming behaviour of attempting to lock in the price at lower or higher levels (e.g. during the so-called honeymoon period after introducing vaccination programmes, which often sees very low levels of incidence).(23)

Our case study showed that, prior to HPV vaccine introduction, a vaccine that additionally protects against anogenital warts is initially estimated to be worth more than a vaccine without warts protection. However, after 10 years of using the warts vaccine, incremental cost-effectiveness analyses starting from the point of re-procurement would switch repeatedly between vaccines at successive re-evaluations if ignoring the temporal inter-dependence of achieved levels of herd protection, and assuming all else staying constant (a common assumption in economics, but often unjustified for vaccinations given that their uptake has been proven to be easily disrupted and difficult to restore).(26-28) As such, although our case study of HPV vaccination saw a disease resurgence indeed start after a few years of switching the vaccine but

taking decades to reach pre-vaccination levels, this is unlikely to be the case for many other close-contact pathogens where resurgences may be seen much more quickly and the avoidable morbidity and mortality may be higher. This is also dependent on the specific disease dynamics given that infectious diseases without or with only a short period of being recovered/immune before becoming susceptible again will return somewhat smoothly to pre-vaccination levels (as in our case study of genital warts), while the dynamics of a disease with a long duration of immunity may lead to large epidemic waves being stimulated over time by the removal of a vaccination programme.(25)

The full benefit of vaccination is generally accrued over a long time by needing to vaccinate sufficient age-cohorts to generate herd immunity.(20) For this reason, cost-effectiveness analyses of vaccination programmes usually have time horizons that stretch into decades, and stopping or changing the programme at short-term intervals could result in failure to achieve much of the predicted long-term benefits of the initial recommendation still to be expected for the time after the re-evaluation. This is likely to be even more curtailed with very frequent re-evaluations and vaccine changes. For instance, regular changes between a broad and narrow vaccine may lead to accumulation of susceptible cohorts who then experience a resurgence of infection not covered by the narrower vaccine, leading to inter-cohort inequities in protection received. Also because the population will contain a mixture of protected and unprotected cohorts, resurgences may occur primarily in individuals at higher risk of complications, or increase the risk of exposure to those who cannot be vaccinated. Frequent changes may also disrupt vaccine uptake, possibly leading to hysteresis (i.e., long-run lower levels of uptake),(28, 39, 40) and associated health loss as seen e.g. in previous pertussis and MMR scares.(26, 27) Conversely, where the same producer makes both a broad and narrow vaccine, using incremental cost-effectiveness analysis may lead to price loading of the narrower vaccine to ensure that the broader vaccine is purchased and at minimal risk that neither vaccine will be purchased once a vaccination programme has been introduced.

Strengths and limitations

This is a methodological paper that used an economic model of intertemporal demand from the healthcare provider perspective knowing that the perfectly competitive market model is insufficient for healthcare but widely used in economics to illustrate ideas and insights.(30) Our conceptual model and the underlying epidemiology have been unspecified for as far as possible to make it broadly applicable and strengthen the ideas of this paper. More generally, the model underlined again the importance of considering indirect effects.(20) As such, our paper aimed to raise awareness for the issues associated with different levels of indirect effects for different vaccines in the context of incremental re-evaluations. Irrespective of our suggested proposal, it seems worthwhile for future guidance on economic evaluations of vaccines to address these issues explicitly.(41) Estimates from our proposal may also be useful even if informing a scenario analysis. Also, situations may be different for long-run reductions in incidence levels without return to previous levels but a new, lower equilibrium, or with long-term oscillating demand.(4, 17, 28, 37, 39, 42-44) Furthermore, although threshold pricing may only reflect the stated willingness to pay (as e.g. explicitly stated with £20,000 per QALY in England and Wales),(33, 34) it does not need to reflect the maximum willingness to pay, particularly if additional factors apart from cost-effectiveness are considered such as equity. Nonetheless, threshold price analyses are common practice to inform policy advisers and as basis for price negotiations e.g. for vaccine tenders in the UK and as suggested for drugs recently in Canada.(29) Also, the threshold price does not intend to prescribe the final price but allows other price mechanisms to take place (such as negotiations, tenders, and competition).

Our case study of HPV vaccination illustrated the key challenges of informing vaccine pricing after having introduced a vaccination programme, a practice that is routinely done in many countries such as the UK. Using HPV vaccination also helped to illustrate the more complex situation of multivalent vaccines, i.e. controlling another disease or strain at marginal extra costs (note that by using net benefits the conceptual model implicitly comprised the cost-effectiveness of mono-valent or multi-valent vaccines, with prices estimated additively).

Although the ideas discussed in this paper may be more broadly applicable, we caution against using our proposal in other contexts than illustrated for indirect herd effects of vaccines. Also, we did not address the related issue of loss aversion when stopping interventions.(45, 46)

Conclusion

Incremental cost-effectiveness analysis can support rationally-designed healthcare systems that optimise health benefit and value for money. For vaccinations, however, the question of how to maintain the achieved levels of herd protection needs to be addressed explicitly in incremental re-evaluations. We propose to always internalise the entire value of the indirect herd effects achieved and still achievable separately from the direct effects and e.g. at constant rates. With the mathematical tools available to quantify the indirect protection of vaccinations, our proposal could be readily implemented. Because of the complexity of the topic, however, disease and economic experts should be involved in discussions around the choice of scenarios and counterfactual comparators well in advance. Otherwise, wrongly switching vaccines may lead to a rebound of incidence and infection levels, hysteresis of vaccine demand, economic inefficiency and welfare loss, and unintended consequences on public confidence in vaccines, (inter-generational) equity in vaccine access, manufacturer pricing strategies, and the long-term benefit of vaccination.

Supplementary Material

Rational for internalising positive externalities: Simplifying illustration using the perfectly competitive market model

The indirect herd protection of non-vaccinated individuals by vaccinated individuals is a prime example for what economists call a "positive externality", i.e. the impact on others external to an action of individuals or firms.(19, 30) The existence of a positive externality (i.e., the indirect protection) results in an inefficient resource allocation in the perfectly competitive market model, with the social optimum as defined by the marginal social benefit, MSB, being at a higher level of consumption of vaccines than implied by the marginal private benefit to individuals, MPB.(30) Although we use the conventional example of perfectly competitive market models to illustrate how externalities can be internalised in prices to address suboptimal pricing decisions, this should not be mistaken as endorsement of the perfectly competitive market model reflecting the healthcare market.(30) In fact, real markets breach the assumptions of the perfectly competitive market model by the mere existence of externalities and information asymmetries,(47, 48) yet it is a useful model to illustrate ideas and insights.

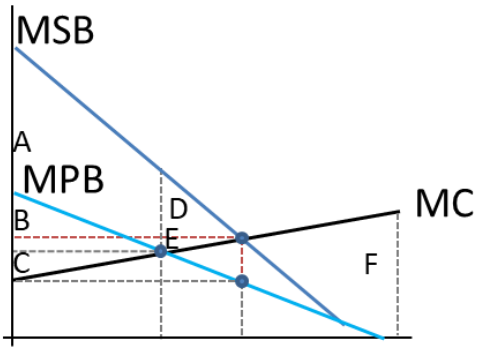
In situations where the MPB is thus not aligning with the MSB an incentive exists for corrective intervention in the form of taxes or subsidies. The idea behind these corrective measures is to internalise the positive and negative externalities so as for individuals and manufacturers to take them implicitly into consideration through higher or lower prices on the side of consumers or producers.(22, 30) For immunisation programmes, the concept of subsidies is frequently used to promote the vaccine uptake of individuals. Under certain conditions, higher prices may hence be economically efficient and welfare increasing.

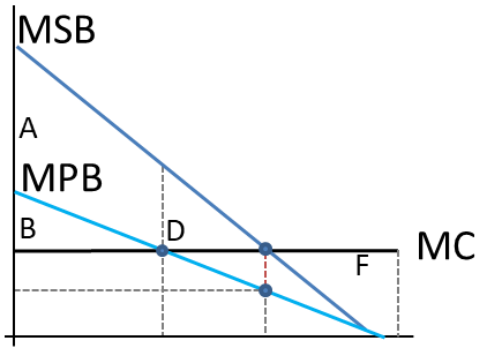
This is illustrated in Supplementary Figure 1; in the perfectly competitive market model the efficient equilibrium price would be where the MPB equals the marginal costs of production, MC. This would generate a consumer surplus of the area labelled with B, and a producer surplus of C. However, in the presence of positive indirect effects, the MSB is higher than the MPB, and not accounting for these positive externalities leads to an economically inefficient resource allocation and welfare loss equivalent to area D+E. Hence, with positive externalities the price

should be equivalent to where the MSB equals MC, incorporating the additional welfare gains for consumers (from higher quantities) and producers (from higher prices and/or quantities). In the perfectly competitive market model this can be achieved through a subsidy, which would shift the MC curve vertically downwards to where it equals the MPB. The subsidy would only consist of the difference between the price where MSB=MC (i.e., the red dashed lines in Supplementary Figure 1), with individuals paying the remainder of the price they were willing to pay at that quantity.(30) Note that the actual size of the subsidy depends on the shapes of the curves; e.g. when assuming the marginal costs to be constant the subsidy may be lower and welfare gains for individuals higher (Supplementary Figure 1, panel b).

Note that a subsidy may also capture the entire price when offering a vaccine at no financial expenses to individuals (i.e., price of 0 for individuals, but of MC for whoever pays the subsidy). All MPB and MSB could then in theory be realised, although there is an irrecoverable welfare loss of area F for paying the subsidy to those individuals who place little to no private value on getting vaccinated (which is why the MPB curve stops short of the end of the horizontal axis; a second-best economic option if not knowing the exact forms and shapes of the curves,(22) although this may not be the case if the herd immunity threshold is high as e.g. for measles vaccination).(19) The figure also changes when considering the demand from a healthcare provider perspective and conceptualising the benefits through pricing;(7, 8) this is illustrated in Figure 1 and Figure 2 of the main text where the values represent the points at which the vaccine prices equal the cost-effectiveness threshold, the demand curves equal the highest net benefit obtained from either vaccine, and the MPB relates to the direct effects only and the MSB to the direct plus indirect effects.

Supplementary Figure 1. The perfectly competitive market model and the rational for internalising positive externalities.


MSB
A
MPB
B
C
D
E
F
MC


MSB
A
MPB
B
D
F
MC

Additional results of the case study

Supplementary Table 1. Long-term economic consequences of HPV vaccination using a warts or a non-warts vaccine during procurement rounds in 2007 and 2017.

	First tender (2007)		Second tender (2017); assumes first tender awarded to warts vaccine			
	Totals over 50 years (2007 – 2056)		Totals over 50 years (2017-2066)		Totals over 60 years (2007-2066)	
	Non-warts vaccine	Warts vaccine	Non-warts vaccine	Warts vaccine	Non-warts vaccine	Warts vaccine
Girls vaccinated with non-warts vaccine (m)	18.06	0	17.21	0	17.21	0
Girls vaccinated with warts vaccine (m)	0	18.06	0	17.21	4.29	21.50
Undiscounted						
Total warts cases (m)	6.49	1.10	4.01	0.21	4.90	1.11
Cost of warts treatment (£b)	0.73	0.12	0.45	0.02	0.55	0.12
QALYs lost due to warts (m)	0.12	0.02	0.07	0.00	0.09	0.02
Discounted (at 3.5%)						
Total warts cases	3.05	0.88	1.05	0.11	1.82	0.89
Cost of warts treatment	0.34	0.10	0.12	0.01	0.21	0.10
QALYs lost due to warts	0.05	0.02	0.02	0.00	0.03	0.02
Price difference for warts vaccine		£116		£77		n/a

b: billion, HPV: human papillomavirus, m: million, QALYs: quality-adjusted life years, UK: United Kingdom.

The “warts vaccine” protects against oncogenic HPV types (16 and 18) as well as HPV 6 and 11 that cause the majority of warts cases, while the “non-warts vaccine” purely protects against oncogenic HPV types and does not protect against HPV 6 or 11. The price difference for the warts vaccine versus the non-warts vaccine was estimated over a 50 year time horizon based on the difference in the net present value of the warts prevention (in terms of discounted costs saved plus discounted QALYs gained times a threshold value per QALY gained of £20,000).

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Figures

Figure 1: Conceptual illustration of changing incidence level over time due to alternating decisions between vaccines, where vaccine A reduces incidence more than vaccine B due to e.g. higher efficacy and/or herd protection that lead to different results in terms of incremental cost-effectiveness (not shown here). Panel a) shows the decision presenting itself at the time of re-evaluation at T_3, panel b) shows potential changes in the incidence level after switching vaccines at T_3 (and possibly repeated switching between vaccine A and vaccine B over T_4 to T_6).

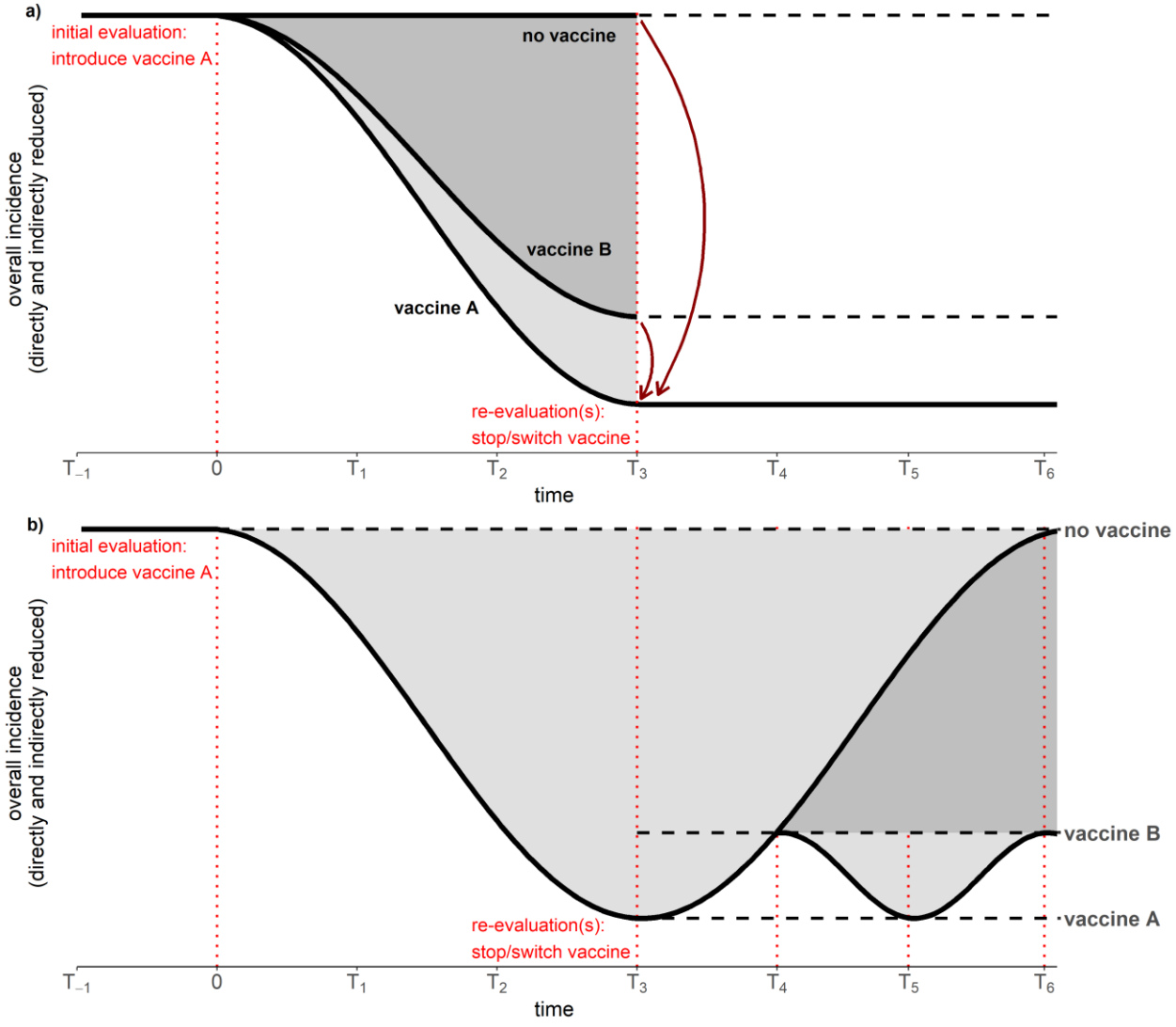
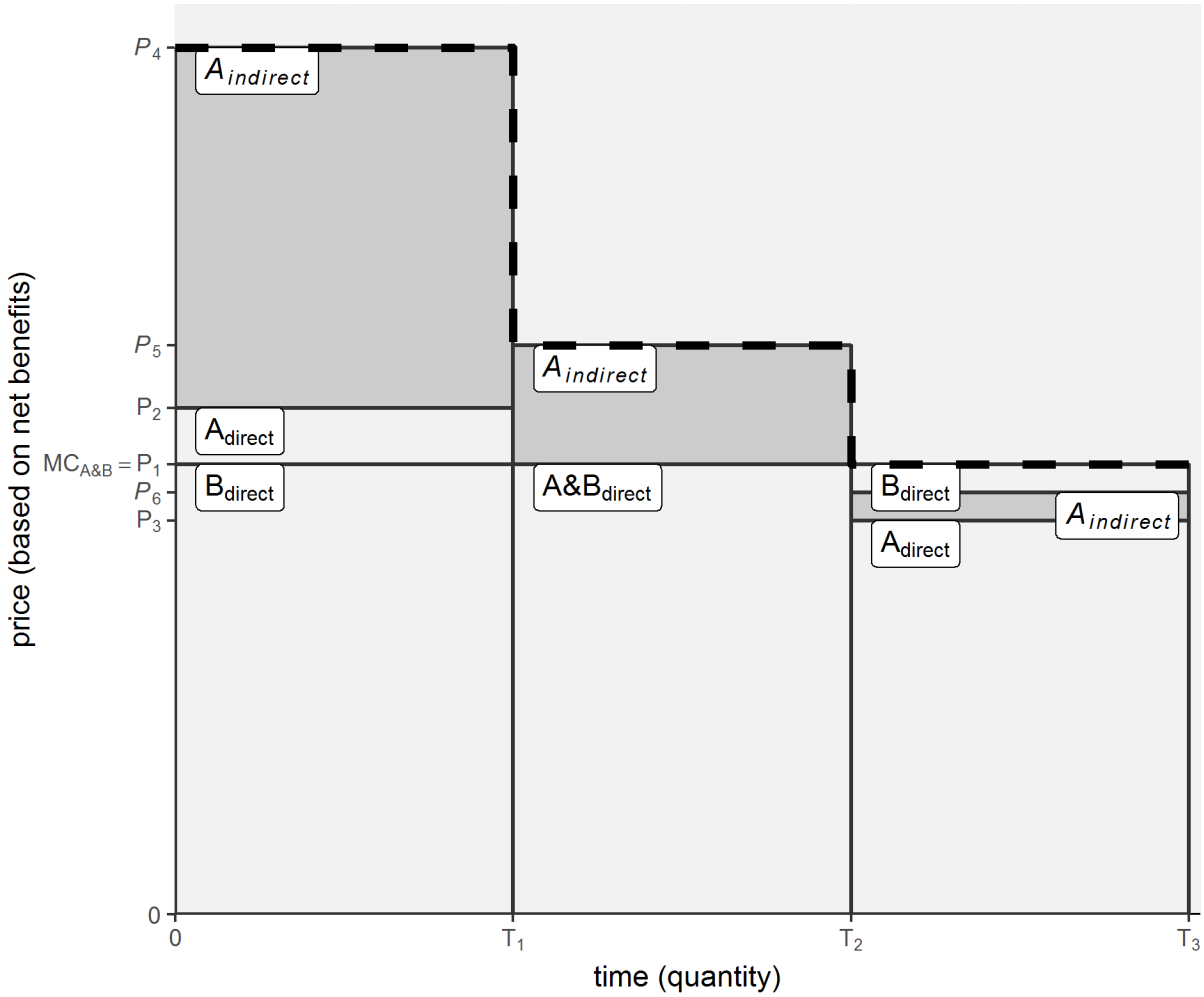
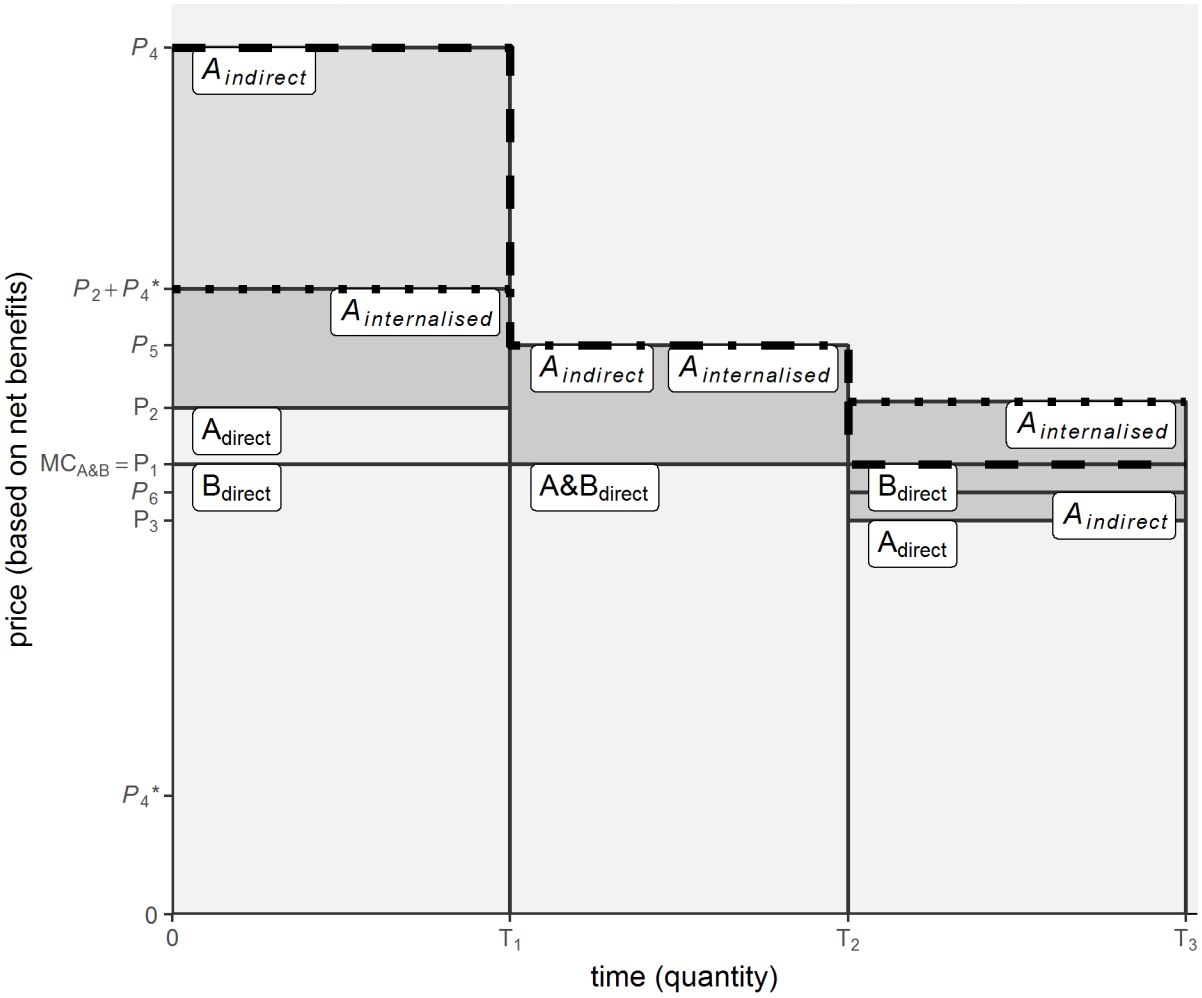


Figure 2: Conceptual illustration of pricing for two mutually-exclusive vaccines A and B over time, and the inter-temporal demand for vaccines of a healthcare provider considering indirect effects (dashed line).



Note: Values of the direct effects start from 0, while values of the indirect effects are added additively.

Figure 3: Conceptual illustration of internalising the indirect effects at constant rates to account for inter-temporal herd protection, and pricing them separately from the direct effects of two competing vaccines A and B.



Note: Values of the direct effects start from 0, while values of the indirect effects are added additively.

Figure 4: Simulated impact on anogenital warts after hypothetically introducing human papillomavirus (HPV) vaccination with a warts vaccine in 2007-2016, showing the persistence of the indirect effects even after ten years when switching to a non-warts vaccine in 2017 but eventual warts resurgence.