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How to Prevent Vaccines Falling Victim to Their Own Success: Intertemporal Dependency of Incidence Levels on Indirect Effects in Economic Reevaluations

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ABSTRACT

Objectives: Incremental cost-effectiveness analyses may inform the optimal choice of healthcare interventions. Nevertheless, for many vaccines, benefits fluctuate with incidence levels over time. Reevaluating a vaccine after it has 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 suboptimal decision making.

Methods: We used a conceptual model of demand to illustrate alternating decisions between vaccines because of time-varying levels of indirect effects. Similar to the concept of subsidies, we propose internalizing the indirect effects achievable with vaccines. In a case study over 60 years, we simulated a hypothetical 10-year reevaluation of 2 oncogenic human papillomavirus vaccines, of which only 1 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 10 years, this differential decreases because of declines in warts incidence, which supports switching to the nonwarts 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 reevaluations, with unintended resurgences, economic inefficiencies, and eroding vaccine confidence. We propose internalizing indirect effects to prevent vaccines falling victim to their own success.

Keywords: cost-effectiveness analysis, decision making, externality, herd immunity, vaccination.

Introduction

Cost-effectiveness analysis is used in many countries to inform decisions about changes to national healthcare programs, such as the introduction of a new intervention or expansion of the population eligible to receive an existing intervention. It may also be used to inform analyses of whether adopting an intervention has been worthwhile and to inform prices that reflect the intervention’s economic value. 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 maximize the net value of an intervention compared with its comparators, that is, the value of the health and economic benefits of disease prevented and alleviated minus the opportunity cost of using the intervention. Nevertheless, 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, if 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 reevaluations of the introduced intervention after some time. In particular, the cost-effectiveness of any change is evaluated incrementally, that is, in terms of the difference in costs and health outcomes of the changed situation compared with the counterfactual. When a change in interventions is evaluated, the counterfactual is keeping the status quo indefinitely. Nevertheless, an existing intervention may already have been used for several years, and, hence, an incremental analysis normally dictates that...
replacing it with a new intervention should be compared with the counterfactual of continuing with the current intervention. The new intervention should then be used instead only if the additional benefit of the intervention is worth the additional price of the new intervention compared with the current one, even if the new intervention is overall cost-effective compared with no intervention. The same principles hold if the decision to continue with a vaccination program is reevaluated decrementally (eg, compared against fewer vaccine doses or no vaccination).

These methods work reasonably well for most healthcare technologies against noncommunicable diseases with little to no impact on others (ie, third parties). Nevertheless, for many vaccines, each infection prevented has the potential to reduce transmission to others—the so-called “indirect effect,” “herd protection,” or “positive externality” of vaccination. This indirect protection is crucial to immunization programs in helping to protect not only the vaccinated individuals but also unvaccinated and vulnerable populations. Ignoring them may result in decisions that lead to economic inefficiency and welfare loss because the social benefits are higher than the direct (private) benefits. Furthermore, the risk of acquiring an infectious disease can vary over the course of a vaccination program, depending on the changing immunological profile of the population, the success of the vaccination program in reducing cases circulating, and other epidemic changes.

Specialist techniques, such as transmission-dynamic models, include the indirect effects of vaccinations. Nevertheless, a vaccine may wrongfully appear less cost-effective in incremental reevaluations 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 reevaluations with rising and falling incidence levels (ie, once enough susceptibles have built up again the herd protection would justify switching back to the first vaccine and so on). Such start-stop or switching decisions are economically inefficient and undesirable given that vaccination uptake is easily disrupted, with potential knock-on effects on public confidence in vaccines, 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 article 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 reevaluations. It first presents some background to illustrate these issues and our proposal from the healthcare provider perspective, before using a hypothetical case study of reevaluating 2 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 2 vaccines. We considered 2 hypothetical vaccines labeled “A” and “B,” and only 1 of the 2 vaccines can be used at any given time (ie, A and B are mutually exclusive). We assume that vaccine A is preferred over vaccine B because of, for example, higher efficacy and/or herd protection. Vaccine A is introduced at t = 0 because it is found to be cost-effective at that time; it reduces overall disease incidence because of direct and indirect protection (cf solid black line over 0-T1). At T1, the cost-effectiveness of the vaccine is reevaluated; vaccine B and indeed “no vaccine” appear to be reasonable alternatives given the low disease incidence (Fig. 1A). In reality, however, this risks ignoring the transient nature of the residual indirect effects of vaccine A because the observed incidence would have been higher had the alternative vaccine B (or no vaccine) been used since t = 0. Therefore, the reevaluation at T1 can lead to 1 of the following 3 outcomes (Fig. 1B):

1. Continue using vaccine A: Resulting in a disease incidence at a continued low level as indicated by the lowest horizontal-dashed line.
2. Switch to vaccine B: Resulting in a disease incidence that rises to a new equilibrium level (eg, because of the lower efficacy and/or herd protection) as indicated by the middle horizontal-dashed line.
3. 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 reevaluations may occur at T4, T5, T6, T7, 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 (Fig. 1B).

Note how the curve of “no vaccine” in T3-T4 is shown symmetrical to T0-T3, and the alternating curve between vaccines B and A over T3-T6 is (largely) symmetrical to the curve at T2-T3; conceptually, the issue can indeed be reduced to moving on the curve depicted between 0 and T1 in a bidirectional dimension, as is commonly done in economics (and also in the figures used in the next sections). In addition, 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 versus 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 intertemporal 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. Note that it is well known that this conceptual model does not reflect reality because of 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 in a perfectly competitive market. Nevertheless, in the interest of generalizability, it provides useful insights for the illustration of ideas. Here, we consider 2 mutually exclusive vaccines A and B again, and we assume that the value of the direct net benefits of vaccine A (ie, 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, for example, because of a higher efficacy...
of A but fewer cases left to prevent with declining incidence (similar to T3-T6 in Fig. 1). For simplicity, the value of the direct net benefits of vaccine B remains 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 preset cost-effectiveness threshold (i.e., the values represent where the vaccine prices equal the threshold of, for example, £20,000 per QALY gained in England and Wales), and the demand curve is equal to the highest net benefit obtained from either vaccine. The supply curve is assumed with the minimal price at which the supplier will generate a return on investment, that is, 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. 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.

Figure 2 illustrates these assumptions and the potential pricing of the 2 vaccines A and B over 3 points in time (depicted in equidistance for simplicity again). The healthcare provider demand for vaccines is shown as dashed line. Then, at 0-T1, vaccine A should be procured over vaccine B given the higher direct net benefits (P2-0 vs P1-0, respectively) and the additional indirect effects with only vaccine A (P4-P2). At T1-T2, the healthcare provider would continue with vaccine A given its lower valued but continued indirect net benefits (P5-P1). At T2-T3, the direct net benefits of vaccine B are expected to be higher than the direct and indirect net benefits of vaccine A (difference of P1-P3 and P1-P6, respectively), and the provider would consider switching to vaccine B when ignoring the indirect effects achieved over 0-T2.

Notably, the positive indirect effects always justify higher prices than the direct effects alone, which conversely translates to lower incremental cost-effectiveness ratios at the price of the direct effects alone. Nevertheless, with marginal costs of P1 for both vaccines, vaccine A becomes unfeasible for the manufacturer and society at T2-T3 (welfare reducing), even when considering the indirect effects at T2-T3 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 buildup of enough susceptible individuals, the horizontal time axis can be interpreted in a bidirectional dimension, that is, the direct and indirect net benefit of vaccine A may rise again (as at T2-T1), justifying a switch back to A if the vaccines were reevaluated once more (and when considering net benefits from indirect effects; otherwise, the switch back would occur when reevaluating at higher levels as seen at T1-0).
Part 3: Proposal Addressing the Intertemporal Dependency of Incidence Levels on Vaccine Demand and Herd Protection

Given that externalities qualify for being internalized in prices (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.03.022), we propose to account for the intertemporal 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 reevaluation. 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 reconsidered because the indirect effects achieved up until the time of reevaluation may over- or underestimate their value in future (depending on the shape of the indirect effects over time; eg, see Boulier et al.19).

This idea is illustrated in Figure 3, where the direct benefits of the vaccines are unchanged (Fig. 2), but the total indirect effects of vaccine A over 0-T3 are internalized with $P_4^*$ (dotted lines). Essentially, this aims to avoid higher prices by reevaluating over the entire timeframe (0-T3) instead of only when indirect effects are high (0-T1) and to avoid lower prices by reevaluating over the entire timeframe (0-T3) instead of only when indirect effects are low (T2-T3), assuming they have been high before (0-T2). Some of the value assigned to the indirect benefits at 0-T1 is, thus, allocated to after T3, which increases prices at T1-T3, leads to vaccine A staying in the market at T2-T3, and A being favored across 0-T3 given its indirect effects.

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 United Kingdom in 200733 and the subsequent switch from a bivalent to a quadrivalent vaccine after a competitive tender in 2010.34 Here, we used the model to estimate the impact of female HPV vaccination on the annual incidence of anogenital warts for illustration purposes only. Although the scenarios we consider are hypothetical, the model has been previously fitted to HPV prevalence, warts incidence, and economic parameters from the United Kingdom. It also illustrates the wide range of vaccines used for infectious diseases that may be characterized 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) and 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 (“nonwarts vaccine”). In this example, the 2 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 10 years.33 The 2 hypothetical vaccines approximate the actual difference between bivalent (Cervarix, GSK, Brentford, United Kingdom) and quadrivalent (Gardasil, Merck, Darmstadt, Germany) HPV vaccines. Nevertheless, 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 nonvaccine types.34

We simulated the potential effect of 2 hypothetical competitive rounds of tendering to decide which vaccine to use in the national schedule: (1) the first round in 2007 to decide on the vaccine to use during 2007 to 2017 and (2) the second round in 2017 to decide on the vaccine to use thereafter. The starting point for the second analysis (the counterfactual) is the epidemiologic situation in 2017, that is, after 10 cohorts of girls had received the warts vaccination with a catchup campaign in the first few years (of note, the United Kingdom 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 for the warts vaccine to be preferred over the nonwarts 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.35,36 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.35,36 We considered wart treatment costs per case for a mean of £11337 and mean QALY losses of 0.018.38 All analyses were done in R software (R Core Team, Vienna, Austria).

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 the warts vaccine is used only until 2017 after which there is a switch to the nonwarts vaccine (the spike in fully vaccinated girls is because of the campaign in the first few years). Of note, even after a switch to the nonwarts vaccine is made, the incidence of anogenital warts continues to decline for a few years because of the continued existence of cohorts of females that have been vaccinated with the warts vaccine. After decades, the incidence of anogenital warts gradually returns to its prevaccination 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 10 years of vaccination disadvantages the warts vaccine in the second tender because even if a switch was made to the nonwarts vaccine, some of the benefits of having used the warts vaccine in the past would still materialize. 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.
Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.03.022 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 more than 32% (from £116 to £77) between the first and second tender, and if a warts vaccine is consistently priced between £77 and £116 more than a nonwarts vaccine (eg, with £100), incremental cost-effectiveness analyses starting from the point of reprocurement would switch repeatedly between vaccines at successive reevaluations when ignoring the indirect herd effects. If this reduction was completely owing to indirect effects, that is, 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 internalizing the indirect benefits. Nevertheless, one could also assume the entire price difference of warts prevention reflecting an indirect effect because the warts may not have been the prime focus for choosing HPV vaccines that target anogenital warts after hypothetically introducing HPV vaccination with a warts vaccine in 2007-2016, showing the persistence of the indirect effects even after 10 years when switching to a nonwarts vaccine in 2017 but with eventual warts resurgence.

Figure 4. Simulated impact on anogenital warts after hypothetically introducing HPV vaccination with a warts vaccine in 2007-2016, showing the persistence of the indirect effects even after 10 years when switching to a nonwarts vaccine in 2017 but with eventual warts resurgence.

HPV indicates human papillomavirus.
cervical cancer prevention. Then, if we account for the different timings of reevaluation 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 internalize the indirect benefits of £116 × 10/50 + £77 × 40/50 = £85. Note that HPV vaccination is a more complex situation because it uses multivalent vaccines that also help to control another disease strain at marginal extra costs. Furthermore, these simulated results are not meant to represent the actual HPV vaccination program in the United Kingdom. Nevertheless, the situation of switching HPV vaccines has some basis in reality, since the United Kingdom introduced Cervarix in 2008 and switched to Gardasil in 2011, both times after competitive tendering.34

**Discussion**

This study showed how initially cost-effective vaccinations may appear less cost-effective over time when ignoring the intertemporal dependency of vaccine demand on the achieved herd protection and observed incidence levels. This happens when a successful vaccination program 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, ie, inherent to empirically observing one of many possible realizations that depend on decisions made in the past).25,39 In effect, the vaccine may become a victim of its own success.

In line with the economic insight that externalities qualify for being internalized in prices22,32 and certain situations being insufficiently captured by current practices,30 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 programs.23,24 In subsequent reevaluations, nevertheless, the indirect effects achieved and still achievable with a vaccine need to be reconsidered (ie, the vaccine demand required to maintain the levels of herd protection achieved in the past and expected in future) because 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 reevaluations may need to be conducted systematically to avoid gaming behavior of attempting to lock in the price at lower or higher levels (eg, during the so-called honeymoon period after introducing vaccination programs, which often sees very low levels of incidence).25

Our case study showed that, before HPV vaccine introduction, a vaccine that additionally protects against anogenital warts is initially estimated to be worth more than a vaccine without warts protection. Nevertheless, after 10 years of using the warts vaccine, incremental cost-effectiveness analyses starting from the point of reprocurement would switch repeatedly between vaccines at successive reevaluations if the temporal interdependence of achieved levels of herd protection is ignored and all else is assumed to stay 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 that a disease resurgence indeed started after a few years of switching the vaccine but took decades to reach prevaccination 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 having recovered or being immune before becoming susceptible again will return somewhat smoothly to prevaccination 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 program.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 programs usually have time horizons that stretch into decades, and stopping or changing the program 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 reevaluation. This is likely to be even more curtailed with very frequent reevaluations 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 intercohort inequities in the 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 (ie, long-run lower levels of uptake)28,41,42 and associated health loss as seen, for example, in previous pertussis and measles, mumps, and rubella 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 program has been introduced.

**Strengths and Limitations**

This is a methodological article 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.32 Our conceptual model and the underlying epidemiology have been unspecified as far as possible to make it broadly applicable and strengthen the ideas of this article. More generally, the model underlined again the importance of considering indirect effects.20 As such, our article aimed to raise awareness for the issues associated with different levels of indirect effects for different vaccines in the context of incremental reevaluations. Irrespective of our suggested proposal, it seems worthwhile for future guidance on economic evaluations of vaccines to address these issues explicitly.43 Estimates from our proposal may also be useful even if informing a scenario analysis. In addition, 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.4,21,39,41,44-46 Furthermore, although threshold pricing may only reflect the stated willingness to pay (eg, as explicitly stated with £20 000 per QALY in England and Wales),35,49 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 the basis for price negotiations, for example, for vaccine tenders in the United Kingdom and as suggested for drugs recently in Canada.25 In addition, 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 program, a practice that is routinely done in many countries, such as the United Kingdom. Using HPV vaccination also helped to illustrate the more complex situation of multivalent vaccines, that is, controlling another disease or strain at marginal extra costs (note that by using net benefits, the conceptual model implicitly comprised the cost-effectiveness of monovalent or multivalent vaccines, with prices estimated additively).

Although the ideas discussed in this article may be more broadly applicable, we caution against using our proposal in other contexts than those illustrated for indirect herd effects of vaccines. In addition, we did not address the related issue of loss aversion when stopping interventions.47,48

Conclusion

Incremental cost-effectiveness analysis can support rationally designed healthcare systems that optimize 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 reevaluations. We propose to always internalize the entire value of the indirect herd effects achieved and still achievable separately from the direct effects and, for example, 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, nevertheless, 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, (intergenerational) equity in vaccine access, manufacturer pricing strategies, and the long-term benefit of vaccination.

Supplemental Material

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