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Assessing Medications' Value

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The Economics of Medicine : Assessing Medications' Value

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FACULTÉ DES SCIENCES ÉCONOMIQUES

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sur le rapport des membres du jury

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Autorise l'impression de la présente thèse.

Neuchâtel, le 25 mars 2014

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Executive summary

Due to the size of health care within the economy, the perceived failure of the system and the uncertainties about spending efficiencies, health care economic evaluations are essential. Two conceptual bases exist to run economic evaluations. We will first take a look at traditional welfare economics and will then evaluate extra-welfarism and social contract for decision-making. Cost-benefit analysis (CBA) is linked to the first approach and intends to replicate a market optimum. CBA compares the monetary benefits and costs of a new health care intervention. Under this framework, health care interventions should be undertaken if marginal social benefits exceed marginal social costs. CBA provides information about allocative efficiency since CBAs are not restricted to the welfare gains from health improvement and can be conducted in all the sectors of the economy. It could, in theory, be used to determine how much a society should spend on health care, education, transportation, etc. Two groups of defenders of CBA can be characterized. One group defends CBA because it attempts to reproduce market outcomes. The other group believes that welfare is utilitarian. More specifically, that social welfare is a function of the sum of individuals' utilities. However, CBA is controversial since it relies on strong assumptions that may not be realistic. A common alternative for payers is to rely on the social contract theory and use a cost-effectiveness analysis (CEA) and budget impact to decide whether a new technology should be adopted. CEA provides information on whether or not the incremental health gain from a new intervention is produced at a minimal cost but does not specify whether the health gain produced matches the individual preferences within the society. In other words, it cannot determine whether a society is producing too much or too little health care. This represents another key difference between CBA and CEA: CBA can help set the budget level while CEA can only allocate a pre-determined budget. A

special case of CEA is cost-utility analysis (CUA) by which health benefits are measured in quality-adjusted life years. The budget impact only provides information on whether or not the new technology is affordable given the budget constraints. If a new treatment has no incremental health benefits, CBA, CEA and budget impact frameworks provide the same answer since only costs savings are considered.

In this thesis, the concepts and tools used for health economic evaluations are reviewed, evaluated and used in real-life examples. For instance, I conducted a cost-effectiveness analysis to estimate the economic value of a potential vaccine against respiratory syncytial virus. In using the framework that would likely be used by payers, the article helps vaccine manufacturers to evaluate the price potential of the theoretical vaccine and help them identify key clinical endpoints. Additionally, I identified some shortcomings and contradictions of current health economics evaluations. More specifically, I evaluated how current methodologies disfavor preventive technologies, such as vaccines, compared to curative technologies, despite arguably being more desirable. In the United States, each insurance company is free to choose a health economic evaluation framework. I studied how significant drug coverage differences can be between insurance companies and therapeutic areas. In particular, I showed, that American health insurance companies ask that patients bear substantial cost-sharing for expensive cancer medicines. This could prove problematic since it could lead to compliance issues. Finally, by surveying preferences in American households, I discovered that the methodologies used to evaluate health care do not necessarily match the preferences of the population, contradicting the foundation of the welfare theory. Finally, I developed a framework that will help to estimate the value of the compounds with limited differentiation from payer, pharmaceutical and societal perspectives. This type of framework is important because 58% of new molecular entities

between 1990 and 2004 were drugs with "therapeutic qualities similar to those of one or more already marketed" (FDA, 2009).

Each of the previous points will be developed in the following sections. In-depth review of economic evaluation theories and methods can be found in the Handbooks in Health Economic Evaluation, Oxford University.

Keywords: Health care economic evaluation, cost-effectiveness, incentives, vaccines, RSV, clinical endpoints, value drivers, research and development, asthma, meta-analysis, me-too, drug formulary, fetal death, stated preference, discrete choice experiment.

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Part I

1. General introduction

The aim of this dissertation is twofold. First, it illustrates how the use of health economics can help a manufacturer make decisions on research and development investments. Clinical trials are by nature, relatively small and do not directly provide the economic and medical consequences of health care intervention at a country level. A health economics model can achieve this objective. Said model can also estimate the impact on the justifiable price (i.e. payers' willingness-to-pay) of a key intervention's characteristics such as mortality. By estimated the relationship between price and treatment efficacy, the manufacturer can calculate the new intervention's expected return on investment. This will help the manufacturer make an informed decision on whether investment is medically important and economically viable. The second aim of this thesis is to identify various market failures and shortcomings from current evaluation frameworks.

The dissertation is divided in two main sections. The first, reviews the various methods used for the economic evaluations of health care interventions. Specifically, I review the theoretical justification of each methodology in addition to their similarities and differences. I will also use case studies that illustrate how particular countries implement these methods in the *real world.* The second section uses a cost-effectiveness framework to show how manufacturers could better evaluate which clinical or economic endpoints should be included in clinical trials. Four additional essays are included which describe the limitations and unintended consequences of current evaluation methods.

2. Background: The need to evaluate healthcare

According to the Organization for Economic Co-Operation and Development (OECD, 2011), health care expenditures grow faster than GDP and now exceed 10% of GDP in a number of developed countries. The United States ranked first in 2009 with 17.4% of GDP spent on 4health care. France is a distant second (11.8% of GDP) followed by Switzerland (11.7% of GDP). Health care expenditures have been steadily growing over the last 23 years in the United States, Japan and large European countries. The United States has experienced the largest increase with 8.3 more GDP points spent on health care between 1980 and 2009. The United Kingdom, Canada, France and Spain also saw substantial increases in health care spending over the same period (between 4.2 and 4.8 incremental GDP points). The return on this health care investment is unclear because the concept of outcome is difficult to measure since conclusions depend on the metrics used, including life expectancy vs. infant mortality vs. gender/income equality. Therefore, health care's productivity, defined as outcome/input, is problematic to estimate. Additionally, a change in the population's health may not be related to the performance of the health care system. For example, the decrease in life expectancy in Eastern European countries in the 1990s was driven by the increase in violent deaths, alcoholism, suicide and car deaths and cannot be attributed to the performance of the health care system (Cornia and Paniccia, 2000). The difficulty in assessing the performance of health care systems may be a reason why the World Health Organization never updated the controversial ranking of health care systems (2000).

Evaluating the performance of a health care system is further complicated by the following market failures:

Imperfect and potentially asymmetric information: Patients have to rely on an agent or physician for diagnosis and treatment since they cannot independently assess whether a health care intervention is medically necessary. However, the physician is not a perfect agent since s/he may recommend unnecessary health care interventions either because s/he is overcautious (e.g. mastectomy is often conducted without being medically necessary) or for financial reasons (namely, to increase income) if s/he is paid fee-for-service. Conversely, the physician may be reluctant to recommend a costly intervention if s/he is paid via a capitations scheme. The informational failings not only lie on what to buy but also on where to buy it. Consumers often rely on personal experience, word of mouth or brand recognition to choose their medical providers or health care institutions. However, unlike cars (Blue Book) or electronics (Consumer Reports) there are no objective tests to assess the quality of service given by a particular provider.

Insurance failure: Another informational failure arises from the fact that patients' true health cannot be perfectly assessed by insurance companies. This leads high-risk individuals to potentially choose more generous insurance plans (adverse selection). And, since health care is not (fully) paid by insured patients, moral hazard is created and leads to healthcare's overutilization. By analyzing the results of the RAND Health Insurance Experiment (HIE), Manning and colleagues (1987) estimated that the expenditures for individuals without any out-of-pocket expenses was 45% higher than individuals protected only with catastrophic insurance. Therefore, health insurance is only second best because it compensates for treatment and not the health loss *per se*. A first best insurance system would be achieved if health rather than health expenditure would be measured. In that case, moral hazard would not exist and risks would be perfectly pooled between high and low risk individuals.

Imperfect competition: Barriers to entry are imposed to ensure minimal level of quality. Those barriers to entry can lead to medical deserts in some rural areas. This could potentially have an impact on quality since patients cannot shop around to identify the best physicians. What is more, physicians are not necessarily compelled to provide the best possible care.

Mixed public goods/externality: In addition to the effect on the individual receiving it, health care can provide external benefits. More specifically, an individual can have a positive impact on others' health by buying health care. This is best illustrated by the herd immunity effect associated with immunizations against infectious diseases.

In order to correct health care market failures and uncertainties, efficiency measures can be imposed with incentive payment schemes (such as Diagnostics Related Group pricing or capitation payment) to avoid supplier-induced demand. A well-known result from the RAND Health Insurance Experiment was that cost-sharing (in the form of deductible or co-payments) could avoid moral hazard without negatively impacting quality. It was found that the optimal insurance policy should have a $200 deductible (in 1983 dollars) and a 25% coinsurance to a stop loss of $1,500 (Newhouse J.P. and the Health Insurance Experiment Group, 1993). Those results supported the use of cost-sharing in health care. Regulation is another tool to manage the health care market. For instance, authorization to open a medical practice can help ensure that demand matches supply. Finally, economic evaluations, defined as a comparison of costs and consequences between alternative treatments options, to improve resource allocation efficiency (Drummond et al 2005). In this thesis, I focused on the evaluations of pharmaceuticals which are an important part of health care expenditure. Pharmaceutical expenditures represent 17.5% of health care expenditures and 1.5% of GDP in OECD countries (OECD, 2008). In particular,

understanding the value of drugs is also critical for payers (e.g. health insurers) when making reimbursement decisions; for physicians and patients when electing treatment choice and allocating healthcare spending; and for society when improving efficiency by directing healthcare resources to the most cost-effective uses. In the following sections, the various types of economic evaluations are reviewed and their objectives, advantages and shortcomings are presented.

3. Cost-benefit analysis (CBA)

3.1. Description and rationale

In a cost benefit analysis, the monetary value of the outcome (i.e. the benefits) and the costs of a health intervention are evaluated. The benefits are the entire populations' utility expressed in monetary terms. If the marginal social benefit *B* exceeds the marginal social cost *C*, the health intervention should be undertaken. CBA provides information on the allocative efficiency (i.e. how to optimally use society resources across various economy sectors) and aims at increasing social welfare (i.e. overall individuals' welfare within the society).

The theoretical justification of CBA lies within the concepts of welfarism, the welfare theorems and Pareto efficiency. Welfarism states that individuals maximize their utilities and by comparing the effect of each state on individuals' utilities, social states can be ranked. Under this framework, a new drug should be reimbursed if the society's welfare is higher than by not reimbursing it. An allocation is Pareto efficient if no individual can be made better off without making another individual worse off. The (simplified) first and second welfare theorems state that free market competition leads to Pareto efficient outcomes. And, that a Pareto efficient allocation can be supported as market equilibrium if the initial endowment is distributed

appropriately. The implementation of CBA results lead to a state closer to a Pareto optimum and, therefore, closer to a market equilibrium per the welfare theorems. More accurately, CBA intends to satisfy the potential Pareto criterion (sometimes called Kaldor-Hicks compensation principle) and forms the basis for ranking alternative states of the economy. The difference between potential Pareto criterion and Pareto criterion is illustrated in Figure 1. The potential Pareto criterion was introduced because there are only very few, if any, policy changes which make no one individual worse off. Under the Kaldor-Hicks compensation principle, the overall net gains allow the individuals whose benefits increase to hypothetically compensate those that have lost out. CBA implements a variant of the potential Pareto criterion in that it places a monetary value of the gains and losses to those affected by a change on health care policy, such as the reimbursement of a new drug. In practice, individuals should be willing to pay (respectively accept) money to compensate for the increase (respectively decrease) in their health. Net gain calculations allow economists determine whether the policy is Pareto-improving. When the level of improvement provided by a new health care intervention is evaluated vs. current health state, CBA is often conducted using willingness-to-pay (WTP) or willingness-to-accept (WTA) which respectively defines compensating variation (CV) and equivalent variation (EV). The concepts of WTP and WTA arise because it is not possible to directly measure the utility u(x) derived, by individuals when they consume x units of a new intervention. Instead, we can measure the indirect utility function $v(p,m)$ where p the price of good consumed by the individual and m is the available income. $v(p,m) = \max u(x)$ s.t. $px \leq m$. If z^1 the new health state, z^0 the current health state, the EV and CV are defined so that: $v(p, m - CV, z^1) = v(p,m,z^0)$ and $v(p, m, z^1) = v(p, m + EV, z^0)$. In other words, term CV is the income that a consumer would need to be compensated with in order to be indifferent between the higher

level z^1 and the current level z^0 and is therefore the willingness-to-pay for the increase in health. If the consumer is endowed with z^1, then EV is the income that yields equivalent utility as consuming at the lower level z^0 and is the willingness to accept. The amount of money that an individual is willing to pay/accept for a marginal change in health is the marginal rate of substitution between wealth and health. Furthermore, it is seen as an indicator of their strength of preference for a good or characteristics of a good. Figure 2 shows a graphical representation of the CV and EV of a new intervention.

The validity of CBA depends on a number of assumptions. In particular: (1) Health can be measured and a monetary value can be assigned to health states; (2) Health measurements can be compared across health states; (3) Marginal utility of income is the same across individuals (i.e. a dollar has the same value for the winners and the losers) for the Kaldor-Hicks compensation principle to function (i.e. a net monetary increase across individuals will necessarily lead a net increase in utility); (4) Welfare changes generated by the health intervention must be small.

Few countries use cost-benefit analyses for health economic evaluations. Out the 15 European countries whose reimbursement system is analyzed by ISPOR, cost-benefit analysis is only reported as a option in Austria.

3.2. Issues with CBA

There are a number of issues with the assumptions associated with CBA. Firstly, it is assumed that health benefits can be evaluated in monetary terms. Secondly, it is unlikely that wealthy individuals have the same marginal utility of income as indigent ones. One consequence is that the compensation principle will not hold. In addition, the pursuit of Pareto optimality is

incomplete (only losers and winners are considered and not the full population) and makes no statement about equity (an efficient equilibrium could be one where a few individuals have all the goods/are better off and the rest of the population has none/is worse off). Similarly, a state where a minimum-wage worker compensates a billionaire for a health gain satisfies the potential Pareto criterion but will likely not be seen as fair by the society.

EV and CV are, in general, different from the true consumer surplus CS at the market optimum EV. Additionally, WTP and WTA methodologies can lead to biases and measurement issues. For instance (attributes can be misunderstood by respondents; respondents may overestimate their WTP since they do not have to pay for their choices they elect).

Distortions (different tax rates for different goods means that individuals do not face the same relative prices in capital markets) are also inconsistent with Pareto optimality.

There are issues with utilities. Specifically, even if goods were distributed equally, the utilities would not be equal across individual. For instance, physical conditions impact valuation. Health should be measured rather than utilities since it is the principal output of health care services.

Finally, there has been reluctance to place some monetary valuation of health and life. For Cookson et al. (2008), the reason may be that a person suffering from a disease is identified as an individual and not as a statistical life.

4. Social contract and decision-making

4.1. Cost effectiveness analysis (CEA)

In societies where the cost of an individual's health care is shared with others (e.g. via taxation), priority setting is essential in establishing "just terms of sharing costs among citizens"

(Weale, 2012) and benefits. The social contract is therefore about identifying the principles upon which "the members of society cooperate with one another in a shared social order" (Weale, 2012). Under the social contract theory, agents such as representatives of the Ministry of Health are in charge of making the justifications in defining the terms of social health contract. Information that helps agents allocate resources "fairly" is required for the agents to make a decision. As such, the focus is often placed on cost-effectiveness analysis since it is difficult to place monetary value on health states, a requirement for CBA.

CEA involves a comparative analysis of alternative interventions (or lack thereof). Costs of different interventions are compared to their (quantifiable) outcomes. Both costs and outcomes are calculated per year, discounted (if the costs or benefits are spread across more than one year) and summed across the relevant investment period. An incremental cost effectiveness ratio is then calculated and compared to a shadow price λ per the following formula:

$$ICER = \frac{Cost_{\text{int}} - Cost_{comp}}{Eff_{\text{int}} - Eff_{comp}} < \lambda \qquad (1)$$

Where $Cost_{int}$ is the cost of the new intervention, $Cost_{comp}$ is the cost of the comparator, Eff_{int} is the benefit of the new intervention, Eff_{comp} is the benefit of the comparator. Benefits can be as diverse life-year gained, case, hospitalization averted or mmHG reduction in glycated hemoglobin. In the CEA framework, any intervention found to produce a unit increase in benefits for a cost lower than λ should be funded.

4.2. Cost utility analysis (CUA)

Often, quality-adjusted life-years (QALYs) are used since they provide a normalization of benefits that attempts to capture in one dimension both the increased survival rate and or its effect on quality of life. It is an important metric since it allows comparisons between disease

states where 1 corresponds to full health and 0 to death (a negative QALY represents a health state worse than death). Therefore, the use of QALYs helps allocate budgets by prioritizing treatments with the biggest "bang for the buck" (productive efficiency).

The World Health Organization used disability-adjusted life years (DALYs) for its Global Burden of Disease studies. DALYs disease weights are the opposite of those used in QALYs with a weight of 1 representing death and 0 full health (Robberstad 2005). DALYs are also age-weighted and give more weight to the life-years of bread-winners and care-takers and less weight to the life-years of children and the elderly (Robberstad 2005). Finally, DALYs were assessed by expert panels and not by patients or samples of the population. When QALYs or DALYs are used, cost-effectiveness analysis is sometimes referred as cost-utility analysis (CUA) (Torrance 1976). In the following section, I will review whether this term is appropriate.

In order to calculate the incremental QALY gained from a new intervention, the health states with and without the interventions must be described and evaluated. Since the objective of CEA is to allocate a budget across multiple interventions, the incremental health gains have to be comparable across interventions. Therefore, a cardinal measure is required. Three main methods are used to directly assess QALYs for a specific condition: the rating scale, the time trade-off and the standard gamble.

Rating scale (RS) or visual analogue scale (VAS)

In the rating scale, the health scale ranges from the worst (or least preferred) to the best (or most preferred) states. Next, a specific health condition is described to respondents who are then asked to place the condition (or their own health) on the scale. If several health states/conditions are rated, the distance between states/conditions indicates the strength of the

preferences. The EQ-5D visual analogue scale is one example of this evaluation method. The best state that one can imagine is marked 100 and the worst possible state/condition is marked 0. Comparison between individuals is complicated by the fact that the best and worst possible states is likely to vary across individuals. A healthy, young individual and a disabled, elderly individual are likely to have different viewpoints about what the best possible state is. The elderly individual probably does not consider full health as the best possible condition. Another issue with the scale is that it does not force respondents to make trade-offs and respondents may overstate their preferences since there is no associated cost.

Standard gamble (SG)

The theoretical justification of the standard gamble is the expected utility theory under which respondents are motivated by the maximization of their expected utility. Under the expected utility theory, when faced with multiple choices, an individual chooses the choice that has the highest expected utility. If the consumer receives x with the probability p and y with the probability 1-p, the expected utility of the gamble is p*u(x)+(1-p)*u(y). Risk-aversion is an important concept in the risk-neutrality: if an individual faces a certain z equal to p*x+(1-p)*y, there are three possible cases/outcomes: if the utility of a certain outcome is the same as that of the gamble outcome, i.e. u(z)=u(p*x+(1-p)*y)=p*u(x)+(1-p)*u(y), the individual is said to be risk neutral. If the utility of a certain outcome is greater, the individual is said to be risk averse. If the utility of a certain outcome is less, the individual is said to be risk-seeking.

In the standard gamble approach, the respondents are presented with two alternatives. If the state to value *i* is preferable to death, living in state *i* will be one of the alternatives (certain outcome). The other alternative is living in perfect health with a probability *p* or facing a certain

death with probability (1-p) (gamble outcome). p is varied until the respondents are indifferent between alternatives one and two (Figure 3). At that point p^o, the valuation of state i is p^o*1+(1-p^o)*0= p^o. The last equation assumes that the respondents are risk neutral. In other words, if U is respondent's utility, then U(alternative 1)=U(p^o*Full health+(1- p^o)*death)= p^o*U(Full health)+(1- p^o)*U(death)=p^o. As a consequence, standard gamble will provide cardinal measure of utility only if individuals are risk neutral.

Time trade-off (TTO)

Similar to standard gamble, respondents are presented with two alternatives, one being full-health. However, time trade-off evaluations do not involve any uncertainty. Instead, respondents select time durations for which they are indifferent between both alternatives. In the example presented in Figure 4, respondents can choose between being in an ill state for 5 years or being in full health for a shorter period of time (X years). X is varied until the respondent is indifferent between being in full health for X years and being in an ill state for 5 years (Figure 4). In that case u(ill state)*5=X*u(Full health) and valuation of the ill state is simply X/5.

If a chronic state is worse than death, the calculation varies slightly. Indifference is actually reached when the respondents is willing to spend X years in full health and 5-X in the worse-than-death state. Then X+(5-X)*u(ill state)=0 and u(ill state)=-X/(5-X)<0. In that case, the valuation of the ill state is not bounded and Torrance recommends to set a minimal value of -1.

Multi-attribute systems (MAS) or indirect methods to calculate QALYs

The disease state's evaluation techniques presented above require a description of the symptoms. This can be cumbersome and the valuation results could be sensitive to the wording used. Multi-attribute systems such as EQ-5D, Health Utilities Index (HUI) can be a solution. The principle

behind such systems is to assess the value of key dimensions (e.g. mobility, self-care, usual activities, pain/discomfort, anxiety/depression for EQ-5D; sensation, mobility, emotion, cognitive, self-care, pain, fertility for HUI-2) describing the health states in which individuals could potentially be. When these values are known, a new treatment's impact on quality of life can be assessed by asking clinical trial participants to complete a MAS questionnaire.

As previously mentioned, the EQ-5D questionnaire is a set of 5 questions. Each question has three potential answers. Overall, 243 ($=3^5$) health states are possible. Dolan and colleagues (1995) presented a sample of the 243 health states to a sample of 3337 British adults who, then, valued the health states using a TTO. By using a regression analysis, it was possible to evaluate each individual component as a deviation from the perfect health status. Similarly HUI-2 has between three and five levels for each attribute. Each level is associated with a utility function. For instance, the best level for fertility ("Able to have children with a fertile spouse") has a utility of 1, the second level ("Difficulty in having children with a fertile spouse") has a utility of 0.97 and the worst level ("Unable to have children with a fertile spouse") has a utility of 0.88. The overall utility associated with this health state is calculated with the following formula: $1.06*b_1*b_2*b_3*b_4*b_5*b_6*b_7-0.06$ where b_x is the score for the level assigned for attribute x.

Acceptable CUA thresholds

Values for acceptable incremental cost per QALY gained have been suggested, but these values are arbitrary and vary widely across countries. For instance, in 2001 the WHO suggested that an intervention should be considered cost effective as long as the cost-effective threshold did not exceed three times the gross domestic product per capita. George et al. (2001) reviewed all 355 submissions, between January 1991 and June 1996, to the Pharmaceutical Benefits Advisory

Committee (PBAC), the recommending body that determines which pharmaceuticals receive public funding in Australia. They found that a product was unlikely to be recommended if the cost per life year gained exceeded Au$76,000 and was unlikely to be rejected in the cost per life year gained was less than Au$42,000 (1998-1999 prices). Historically, the National Institute of the Clinical Excellence (NICE) did not have an official threshold. However, Raftery (2006), after reviewing 86 NICE guidances between 1999 and 2005, concluded that the highest cost per QALY accepted by NICE was £39,000 (for riluzole). NICE now classifies non-cost effective interventions between £20,000 to £30,000. Grosse et al. (2008) reported that an intervention is usually seen as cost-effective if the cost per QALY gained is below $50,000 and not cost effective if the cost per QALY gained exceeds $100,000 in the US. However, Chesson (2011) showed that meningococcal vaccination for adolescents is recommended with a cost per QALY gained of $160,000.

4.3. Issues with valuation methods

As mentioned above, CUA relies on the evaluation of health states by respondents via multiple valuation methods. Issues could arise from two problematic sources: (1) respondents cannot (or do not) report their true health but report their perceived health; (2) different valuation methods provide different results. This section explores those potential issues.

Self-reported health: For Sen (2002), self-reported measures of health, which is the basis for QALYs, can "thoroughly mislead public policy on health care and medical strategy". Sen showed that the self-reported morbidity is higher in the US than in India. Therefore, if one were to rely on self-reported health, the United States seems to have higher health needs than India. This is not the case when longevity data is examined. Sen advances the explanation that

individuals with poor health and less education have a lower perception of illness. Therefore, self-reported health suffers similar problems/constraints to utility (e.g. the poor desire less health improvement).

Consistency between measurements: A number of studies have compared the results obtained via different methods and the evidence of consistency is mixed. Tengs and Lin (2003) conducted a meta-analysis of articles reporting quality of life weights for stroke. 20 articles evaluating 53 weights were reported. Their meta-regression found that the severity of a stroke and the bounds of the scale were significant predictor of the quality of life weights. However, the evaluation method had no impact. Conversely, Hallan and colleagues (1999) asked a sample of 158 health individuals to rate the quality of life of different outcomes after strokes by using RS, SG and TTO. They found that the RS yielded much lower utility estimates than the TTO or SG. Similarly, Daly and colleagues (2000) used a questionnaire that incorporated different techniques of measuring QALYs and found that the valuation of mild symptoms of menopause was 0.65 (95% CI: 0.61-0.69) with the RS. The evaluation was significantly lower than the valuation with TTO (0.85 with 95% CI: 0.80-0.90). Inconsistency between measurement and the wide range of weights is clearly a limitation in CUA because the cost-effectiveness response of a new intervention may vary based on the methods/publication used. Tengs and Wallace (2000) identified 54 documents presenting 1,000 QOL weights and found a considerable variation in the weights assessed by different authors for the same health state.

Cardinal measure of utilities assumptions: Another issue with measurements resides in the notion of cardinal measures of utility which is unlikely. The time-trade-off analysis assumes that if an individual equally values three years in full health and 6 years in imperfect health, he

should also equally value 6 years in full health and 12 years in imperfect health (so called constant proportional time trade-off**)**. If this assumption does not hold, health states would be valued differently based on their durations. However, the constant proportional time trade-off is unlikely: Attema and Brouwer (2010) conducted a literature review showing that most studies reported a violation of the constant proportional time trade-off assumption. As discussed in the standard gamble paragraph, standard gamble will provide cardinal measure of utility only if individuals are risk neutral over QALYs. However, individuals are likely to be risk averse over health which affects the standard gamble measurement.

Identifying the appropriate respondents. Several groups of individuals could provide health states' valuations: patients who have personally suffered from the disease, experts who have the clinical knowledge of the disease or the general public. Nord and colleagues (1999) argue that patients should be the primary source of information since they have first-hand knowledge of the disease and, unlike the general population, there is no risk that they would misunderstand the description of the disease. However, it is impossible to ask dementia patients or infants and small children about their diseases and symptoms. The main argument for surveying/asking the general public is that health care prioritization between interventions is made for the entire population. Furthermore in most developed countries health care is financed by the general population. One drawback in asking members of the general population is that most respondents do not have first-hand experience with the disease or may not understand the definition of the disease. Evaluation by the population is preferred by NICE and in the US. This approach was also taken in one of our articles although I also identified whether the valuation varied for respondents who experience a specific condition (namely the loss of an unborn child).

Difficulties in measuring small health variations: Patients completing an EQ-5D questionnaire, which is the reference for NICE in the UK, have only three options for each of the categories describing their health. Therefore, a new intervention may not show an improvement if the benefits are not sufficient to move up one category. As a consequence, an intervention that provides small benefits to many people may be seen cost-effective even if the total number of QALYs saved are, in theory, substantial.

4.4. Link between CBA and CUA

In case of budget constraints, projects with positive net benefits may not all be undertaken and, therefore, must be prioritized in terms of cost-benefit ratio to ensure that the available resources are directed towards the policies with the highest welfare improvement. In that case, cost-benefit and cost-utility results may be very similar.

Extra-welfarists argue that health rather than utility is the most relevant outcome when assessing the social welfare function (Culyer 1989; Brouwer et al. 2008). For them, maximization of health (such as QALYs), subject to the budget constraint, is the basis upon which states of the world (alternative resource allocations) are ordered. The maximization of QALYs subject to a health budget reveals an implicit valuation of a QALY and a WTP λ per QALYs and could be assessed. More specifically, health care interventions could be ranked based on the cost per QALY gained from reimbursed interventions. The threshold λ would be the ICER of the least efficient intervention currently provided (NICE, 2007). Equation (1) that drove the decision to accept a new intervention is equivalent to $B>C_\lambda$ *w*ith $B=Eff_{int}-Eff_{com}$ and $C_\lambda=\lambda\cdot(Cost_{int}-Cost_{comp})$. Therefore, it is tempting to assume that the results from CEA could be re-expressed in CBA. However, in order to do so, QALY have to adhere to axioms of expected

utility. Pliskin et al. (1980) showed that QALYs are a valid cardinal utility function if three conditions are true: (1) constant proportional time trade-off. ; (2) mutual utility independence (in particular, the fraction of the utility of full health for any state is the same at year one, two, three and the utility results will be the same regardless of the number of years the measurement is taken); (3) risk neutrality (risk preference should be independent of the health state and utility function exhibits constant proportional attitude to risk). For graphical illustrations of these three assumptions, see the work of Johannesson (1994). The previous section (Issues with valuation methods) already described that literature shows the constant proportional time trade-off is often violated. Also, many individuals are risk-averse. Therefore, economic evaluations based on QALYs are not measuring preferences and are not supported by welfare-based notions of efficiency.

4.5. Dealing with uncertainty

A cost-utility analysis can require multiple inputs to estimate the cost of the disease, the current burden of illness and the impact of new treatments. Not all potential endpoints relevant in an economic evaluation can be captured in a clinical trial. Since the size of a trial rarely exceeds a few thousand patients, a rare event may not appear in either the test or the control group. More specifically, the clinical trial may not provide any information on a new treatment's impact on rare events: a sequel may only appear many years after the disease occurred. In that case, a clinical trial may already be closed and will not provide any information on the reduction in sequelae. In addition, estimates from the literature are not always consistent with one another especially if the studies focused on different patient populations. One way to deal with this issue is to conduct a probabilistic sensitivity analysis (PSA). A distribution is assumed for each input

in the model and the cost-effectiveness of a new intervention is calculated for numerous simulations of values drawn from those distributions (Monte Carlo simulations). PSA only partially addresses the issue of uncertainty. The research still has to assess the distribution to be used in the model. A systematic review and a meta-analysis can help close the evidence gap. They synthesize the existing evidence that may not appear in a clinical trial. In one article, I showed how a meta-analysis can help synthesize the available information and determine the appropriate distribution in the model. However, if the studies are heterogeneous, the researcher will still have to use his/her judgment to decide on the values to use.

4.6. Alternative evaluation methods

In some systems, the agents in charge of evaluating health care interventions do not want to engage in any comparisons between benefits and costs. Therefore, cost-effectiveness or cost-benefits analysis become irrelevant. When deciding between two therapies treating the same conditions, health authorities could decide to select the one that minimizes costs. Drummond et al. (2005) intended for this evaluation to compare two options that have the same impact on health outcome but this could be conducted for any comparison of treatments. However, to our knowledge, no western countries use such a method because it fails to take into account the medical benefits that are not associated with health care cost reduction. In particular, this method would reject treatments that prolong life if the additional life-years gained have associated medical costs. Instead, authorities sometimes prefer to consider medical impact and cost impact separately.

5. Evaluation methods used in various countries

United Kingdom: In Scotland, the Scottish Medicines Consortium (SMC) and in Wales, the All Wales Medicines Strategy Group (AWMSG) are in charge of providing cost-effectiveness recommendations. In England and Wales, the National Institute for Health and Care Excellence (previously known as the National Institute for Health and Clinical Excellence - NICE) provides guidance on the cost-effective use of medicines. NICE evaluates drugs referred by the department of health. More broadly, NICE provides national guidelines for "the promotion of good health and the prevention and treatment of ill health." By law, the National Health Service has to find funding for interventions that are recommended by NICE. NICE bases its evaluation on cost per QALY gained. Typically, for a new intervention to be recommended, the cost per QALY should not exceed £30,000.

NICE's recommendations are not without controversy. The decision not to recommend an expensive drug for advanced renal cancer triggered an intense public debate and lead to a special appraisal of treatments "designed to extend life, at the end of life for small populations" (Chalkidou, 2013; NICE, 2009). In order to be considered, the treatment needs to be indicated for patients with all three of the following criteria: (1) a short life expectancy, (2) extend the life of the patient by at least three months compared to alternative therapies and (3) be indicated for small patient populations. For those treatments, the ICER may exceed "the upper end (£30,000) of the range normally considered". Chalkidou (2009) reviewed the decisions of the 13 technologies where end-of-life review was considered between January 2009 and September 2011. Out of the 13 technologies, NICE considered that nine qualified as end-of-life treatment (i.e. met all three criteria). Out of those nine treatments, three were not recommended and six

were recommended. The ICER for the recommended treatments was between £31,800 and up to £50,000 per QALY gained.

France: When evaluating new treatment options, the French health authorities first make a technical assessment of the medical benefits based on five criteria: efficacy and safety, position of the medicine in the therapeutic strategy and the existence or absence of therapeutic alternatives, severity of the disease, type of treatment (preventive, curative or symptomatic) and public health impact (ISPOR Global Health Care Systems Roadmap). Then, the incremental medical benefits vs. existing therapies are assessed. Pricing (i.e. costs) discussions take place only after the medical assessment is made. The price of new technology is negotiated with manufacturers based on the level of incremental medical benefits, the price of local comparator, international price comparison and budget impact. The budget impact of new technologies (incremental technology costs net of any other savings) includes sales forecasts for the next three years, predictable conditions for use and the size of the target population.

Germany: Since January 2011, the Pharmaceuticals Market Reorganisation Act (Arzneimittelmarkt-Neuordnungsgesetz, AMNOG) fixes the rule for pricing and reimbursement of new medication. This law marked a clear departure from the free pricing rule that previously existed and was aimed at limiting the cost of new pharmaceuticals in Germany (GKV-Spitzenverband website). After launch, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) assesses the additional benefits of new pharmaceuticals. If the committee deems that the new therapy does not have any additional benefits compared to comparative therapies (identified by the committee), the reimbursed price is determined based on the price of products with comparable ingredients and/or comparative therapy. If the product has additional benefits, the German evaluation is intermediary between the cost-effectiveness

countries such as the UK and the countries that do not use cost-effectiveness analyses in a systematic way such as the US. The approach is based on an article that was developed by Caro et al. (2010). The authors recommend the use of efficiency frontiers for health economics evaluations. The net costs and additional benefits of an intervention are compared in the context of relevant other interventions in that indication.

The efficiency frontier is drawn in a two steps process: (1) the costs and the benefits of all relevant alternative therapies for a specific disease are plotted on a graph with the benefits as a y-axis and the net costs as an x-axis (see figure 5); (2) the efficiency frontier is determined by drawing the envelope of those points. A new intervention that lies above the efficient frontier is deemed cost-effective. The price for which a new intervention is on the efficiency frontier represents the maximum reimbursable price. Contrary to cost-effectiveness analysis, all relevant benefits are not calculated in a single metric that can be compared across therapeutic areas such as QALYs. The advantage of this approach for policy makers is that it avoids valuing life in economic terms. In addition, it helps to evaluate the price premium a new drug with additional benefits can demand. However, the efficiency frontier faces several limitations. Given the impossibility to compare disease areas with each other, it can only help answer productive efficiency *within* a therapeutic class. It does not help answer whether more or less funding should be allocated to some therapeutic classes. Even within the same therapeutic class, the allocation may depend on the endpoint considered. For instance, multiple efficiency frontiers are drawn if multiple outcome endpoints are relevant for a disease. Each efficiency frontier may provide a different maximal reimbursable price.

USA: According to Fingertip Formulary® (Fingertip Formulary LLC, Glen Rock, NJ), there were 1,768 health plans in the United States in 2011. Each plan is free to make a

reimbursement decision based on its own criteria and there are no reimbursement rules that apply to all plans. That said, budget impact always tends to always play a role.

Potential drivers for the choice of methodologies: The evaluation methods and the extent to which they apply to a whole country depend on whether or not a country considers health care as a public good. Public goods are those that are shared, whose benefits are available to all (e.g. they are non-excludable goods). The consumption of a pure public good by one individual is also assumed not to prevent the consumption of the good by another individual (a public good is non-rival in consumption). Pure public goods are not open to market competition. This is the case for national defense and police work that are usually managed by governments. Private goods such as food and cars, are rival in consumption (one good can only be consumed once) and excludable (e.g. by denying to sell them). Club goods (e.g. cinema) are non-rival in consumption and excludable. In other words, club goods are available to those who are members of the clubs and once you are a member of the club, you have full access to the goods (regardless of others' consumption). Common goods are rival in consumption and non-excludable. Health care is neither a pure private good nor a public good. However, the individual receiving health care is its primary beneficiary and every member of the community gains when others are in good health. For instance, in the case of infectious disease, preventing the infection of one person can prevent the infection of others. In that case, health care acts as a public good (Smith R. et al 2003). Major European countries consider health care as a public good and have government-run health care systems that are heavily regulated. Governments must prove to electors that money is wisely spent which justifies health care economic evaluations. The US tends to consider health care as a private good and, therefore, leaves the market to decide which products should be reimbursed. In other words, externality is not considered sufficient to justify using the economics of the market.

A notable exception is infectious disease where the Advisory Committee for Immunization Practices (ACIP) determines which vaccines should be used and reimbursed.

6. Market failures

6.1. Access to medication

Different methods of evaluation lead to different levels of access to drugs across countries. For example, in 1999 all parents residing in the UK could be reimbursed for the meningococcal C vaccine. In France, parents had to wait until 2009. NICE did not recommend Gleevec (imatinib) against gastrointestinal stromal tumors (GIST) in the UK but the treatment is reimbursed in France. While differences in epidemiology could justify the delay in vaccination reimbursement, a cancer patient living in the UK likely finds it unjust to be denied reimbursement for a drug he would receive if s/he were living in France.

Even within the same country, patients' out-of-pocket expenses may vary dramatically. This is the case in the US. In one essay, I show that eldery patients have access to plans with substantially higher out-of-pocket expenses than individuals who receive insurance via employment. Local environments and constraints can affect access to medications. For instance, 152 primary care trusts (PCT) were responsible, until 2013, for allocating health care budgets and planning health care in the UK. The PCTs had different budgetary constraints or objectives and may implement the NICE recommendations differently. Therefore, even if a national body recommends the use of a new medicine, there might be a so-called "postcode prescribing".

As described above, access to medicine can be contingent on the advice of recommending bodies. For instance, the English and Welsh experience a so-called NICE

"blight", meaning that physicians or local primary care trusts (PCT) will defer prescribing new medications until after the NICE guidance is published. This could delay the utilization of new medicines by months. This lead the UK government to pass legislation in 2009. The three-year, £25-million program allows patients with rare diseases to access medication not yet evaluated by NICE.

6.2. Myopic view

It has been argued that the vaccine market is not attractive to manufacturers because it represents only 2% of global pharmaceutical sales (2002 figures) (Berman and Giffin, 2004). In one essay, a mathematical model was developed to elucidate whether the methodologies used to evaluate new technologies favor drugs over vaccines. By analyzing the interactions between manufacturers and payers, we modeled manufacturers' decision-making process when deciding whether to invest in a vaccine or a drug to combat a disease affecting children.

6.3. International price reference system

In addition to / instead of cost-effectiveness and cost benefit analyses, countries also use the prices used in other countries. In fact, this is the most prevalent way to control costs. More than 75 countries in the world use some type of international price reference when setting the official list price of medicines. The rules and the baskets of reference used by countries vary greatly. The average and the lowest price of the basket tend to be the most common rules. International price reference has led to a convergence in prices, especially among EU countries (see Figure 6). Price discrimination across countries is now difficult to achieve and pharmaceutical companies tend to set a unique price across all European countries. The supposed advantage of international pricing, advanced by the EU commission, is to ensure that all countries benefit from a low price.

Based on the economic theory, a uniform price across markets leads to loss of consumer surplus. An illustration of a potential analysis is shown in Figure 7. The example compares what occurs when manufacturers can set an individual price in each country versus when there is one price across markets. In this illustration, the least price sensitive country benefits from a unique market price. However, patients in the smaller, most price sensitive markets suffer from international price reference since patients incur a higher price. In Figure 7, the profits of launching in market 1 alone are similar to launching in markets one and two with a unique price. The manufacturer may decide not to launch in the smaller, price-sensitive country.

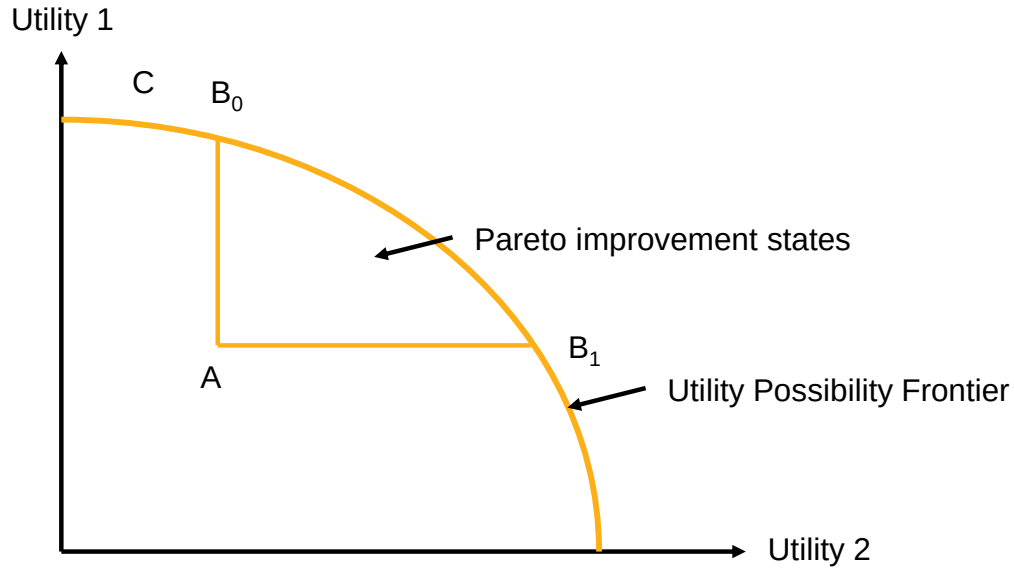
Pharmaceutical companies also offer rebates off the official list price in order to gain access or substantial market share. These rebates are typically kept confidential but, recently, for reasons of transparency some countries and organizations (such as UNICEF and the United Kingdom) have disclosed or have considered disclosing the rebate offers. What could be the unintended consequences of such decisions? We expect that prices will increase where prices/rebates are disclosed. Since they could negatively impact the sales in other countries, pharmaceutical manufacturers will view less favorably the countries where the prices are disclosed since they could negatively impact the sales in other countries.

In the previous sections, various economic evaluations were presented. Table 1 shows the summary of the main methods used. CBA is attractive from an economic theory standpoint but has many limitations. As a result, CEA are more often conducted than CBA. In the last 10 years, 6,597 articles with a title containing “cost-effectiveness” were published in PUBMED (query run on October 3 2012). 1,252 articles containing “cost benefit” or “willingness to pay” or “willingness to accept” in the title were published over the same time period.

Table 1: Summary of economic evaluations

Analysis	Benefits measurement	Results	Potential results comparability
Cost-minimization	Not applicable	Cost comparison ($)	Difficult across sectors of the economy
Budget impact	Improvement of therapeutic benefit (no common definition)	Budget increase/ decrease ($)	Difficult across sectors of the economy
Cost-effectiveness	Natural units, e.g. pain free days, life years gained, hospitalizations avoided	Cost/unit of consequence (e.g. cost/LY gained)	Difficult across therapeutic areas
Cost-utility	Single or multiple effects combined into a weighted index such QALY (valued as "utility")	Typically cost/ QALYgained	Across therapeutic areas
Cost-benefit	Single monetary benefits	Net benefits ($)	Across sectors of the economy

Figure 1. Pareto criterion and potential Pareto criterion illustrated for 2 persons (1 and 2)



Interpretation: Initial state is A. All the states located on the utility possibility frontier (UPC) between B_0 and B_1 are Pareto improvements to A (in the sense that both individuals 1 and 2 have higher utilities than in state A) and are Pareto optimum (no other state can improve the utility of one individual without decreasing the utility of the other one).
Potential Pareto criterion considers state C as an improvement to state A even though person 2's utility is lower in state C than in state A. The reason is that the increase in utility of person 1 far exceeds the decrease in utility of person 2.

Figure 2. Compensating variation (CV) and equivalent variation (EV) of a new intervention increasing utility from u_0 and u_1

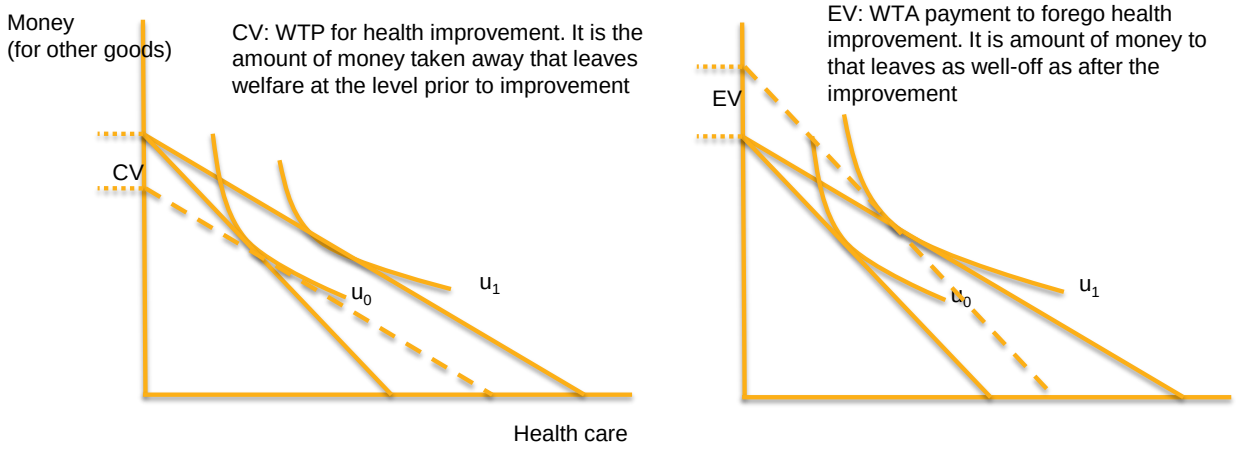


Figure 3. Standard gamble evaluation

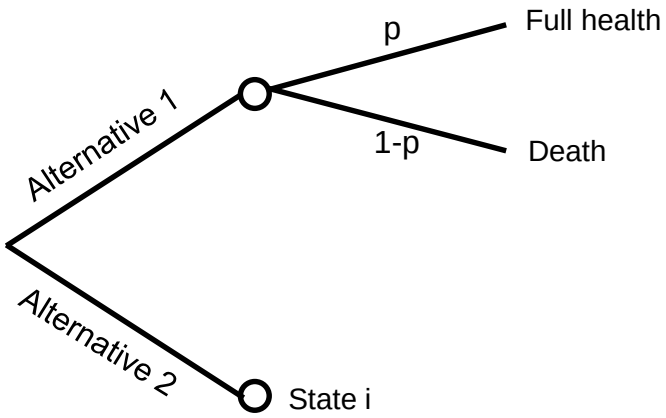
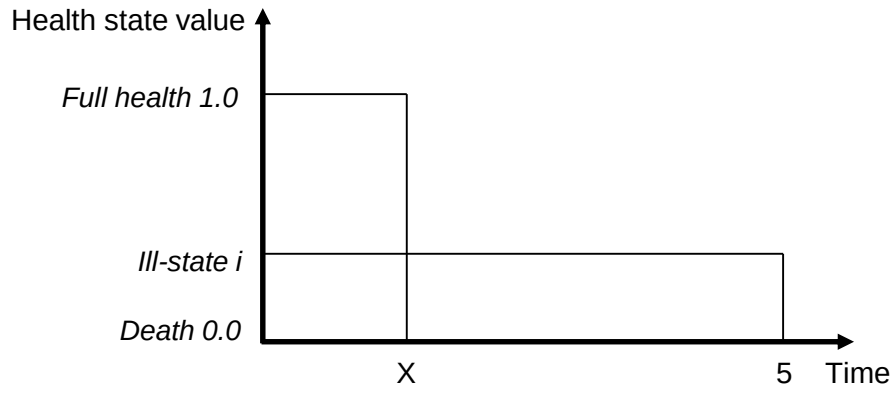
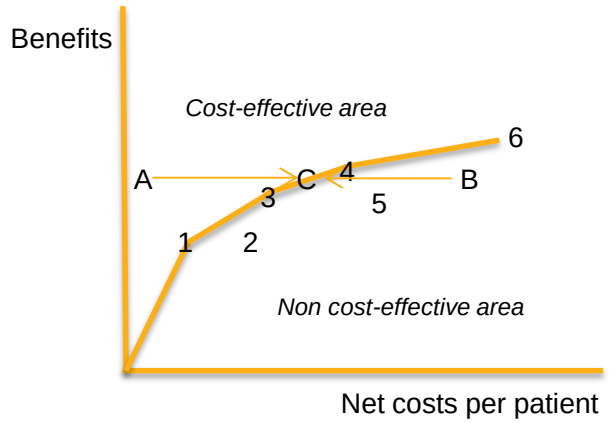


Figure 4. Time trade-off illustration



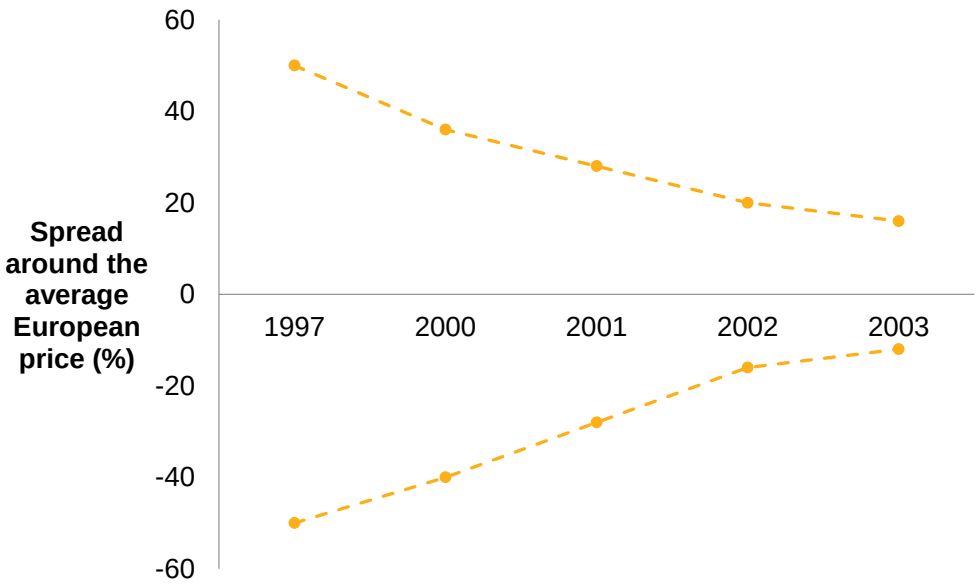
In this example, an individual is indifferent between spending *X* years in a full health and 5 years in a state *i*. The utility of state *i* is X/5.

Figure 5. Efficiency frontier



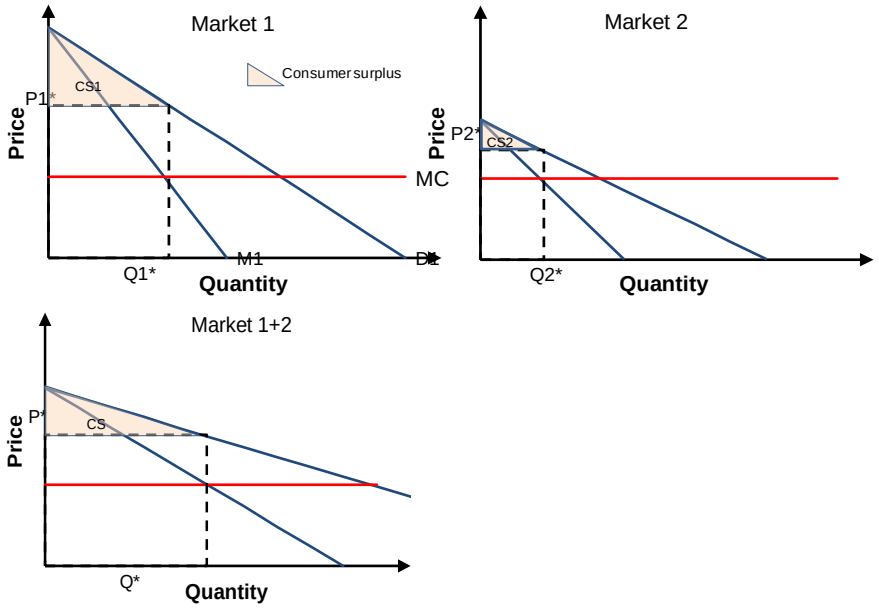
In this example, there are 6 products available to treat a disease. The line linking products 1, 3, 4 and 6 constitutes the efficiency frontier. Products 2 and 5 are below the efficiency frontier and not deemed cost effective. The price of a new intervention has to be set so that the product lies on or above the frontier. A new intervention has a defined set of benefits and is on a horizontal line in the graph above. The position on the line depends on the price of the drug. If the price is "high" (point B), it will in the non-cost-effective area and the drug will not be reimbursed. If the price is low (point A), it will be very cost effective but the manufacturer will not accept the price. Point C is where the manufacturer and the regulator can agree on the price.

Figure 6: Price corridor in European markets



Adapted from IMS Consulting (analysis covering new molecular entities launched by top 13 pharma companies)

Figure 7: Impact of setting the price across 2 countries vs. one country only



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Part II

Empirical Essays

This thesis is composed of six empirical essays that assess different aspects of health economic evaluations, from the manufacturers, payers or the general population's/societal perspectives. In the first essay, a health-economic model simulating RSV-vaccination of infants in the United States was created. More specifically, the impact of efficacy, duration of protection and start of protective immunity was analyzed. Additionally, the impact of value drivers (e.g. cost impact and QALY gained from the reduction in medically attended events, productivity gained and reduction in sequelae) on price was calculated. Those analyses could allow manufacturers to determine which endpoints should be included in clinical trials. The existence and the quantification of a relationship between RSV infections in infancy and wheezing/or asthma in later life have significant implications for the evaluation of new treatments against RSV infections. Therefore, in the second essay, a meta-analysis of the existing evidence was conducted and the results were used in the RSV health-economics model. The third essay analyzes the differences in drug coverage between health insurance plans in the United States. America's health insurance is extremely fragmented and is offered by numerous plans. Each plan has the freedom to decide drugs' reimbursement rate (e.g. co-payment level). This essay provides insight into whether the segments of the population that do not have access to several types of insurance (e.g. elderly patients) face systematically higher cost-sharing schemes. Since there are no economic evaluation guidelines describing how the prevention of a fetal death should be evaluated, the fourth essay aims to illustrate how a healthcare intervention that may reduce the

number of fetal deaths should be evaluated. In order to assess the population's view, a web-based survey of Americans over 18 years of age was conducted. The fifth essay assesses the value of drugs that provide limited incremental therapeutic value over existing products. Those drugs are often referred to as 'me-too' drugs. If a new medication does not have any incremental medical benefits, it will only have economic value if it is priced at a discount vs. similar products that are already on the market. An analytical framework based on empirical data was created. Payers and pharmaceutical companies could use this framework to evaluate drugs with no or limited differentiation. The last essay shows that curative treatments tend to be favored over preventive treatments.

Respiratory Syncytial Virus Immunization Program for the United States: Impact of Performance Determinants of a Theoretical Vaccine.

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Abstract

Objectives: To inform strategic decisions on respiratory syncytial virus (RSV) vaccine development and identify critical endpoints likely to drive the vaccine's medical and economic impact.

Design: A decision-analysis model populated using healthcare utilization data and costs from the literature; vaccine efficacy and duration based on assumptions.

Setting: Vaccination in the physician office setting in the USA.

Participants: A hypothetical cohort of newborn infants.

Intervention: Vaccination of children at low and high risk of respiratory sequelae with a theoretical RSV vaccine vs palivizumab prophylaxis for children at high risk.

Outcome measures: Medical and economic value of RSV vaccination, including cost per quality-adjusted life-year (QALY) gained.

Results: Using base-case assumptions (efficacy 50% at birth; half-life 12 months), RSV vaccination would prevent 23,069 hospitalizations and 66 deaths per vaccinated birth cohort in the USA. Excluding vaccination costs, direct medical costs for RSV would reduce by $236 million, and income and productivity losses by $134 million. Assuming a vaccine cost per course similar to Rotarix® in the USA ($232 including administration fees), the cost per QALY gained would be $93,401 (95% CI: $65,815–$126,060) from the healthcare system perspective and $65,115 (95% CI: $41,003–$93,679) from the societal perspective. The net cost (healthcare system perspective) per life-year saved would be $216,120 (95% CI: $161,184–$263,981); the cost per hospitalization averted would be $19,172 (95% CI: $14,679–$22,093). Aside from

efficacy, the vaccine's impact is sensitive to the start of protective immunity and the duration of protection.

Conclusions: Development of an RSV vaccine would substantially reduce inpatient hospitalizations and outpatient visits. It would also have an impact on infant mortality. To demonstrate the full medical and economic value of the vaccine, appropriate endpoints or endpoint surrogates for hospitalization, mortality, and total case reductions should be collected during vaccine development.

Introduction

Respiratory syncytial virus (RSV) is the most common cause of severe lower respiratory tract disease among infants and young children [1]. 69% of infants are infected during the first year of life and 83% during the second [2]; typically, <3% experience severe symptoms and require hospitalization [3].

Globally, there are 34 million (95% CI 19·3–46·2) new RSV infections annually in children <5 years old, with at least 3.4 million (95% CI 2·8–4·3) infections necessitating hospital admission, leading to 66,000–199,000 deaths [4]. Infants and children who suffer from severe RSV infections may be susceptible to the development of respiratory sequelae such as wheezing or asthma [5]. Groups particularly at risk include premature infants and children <2 years old with chronic lung disease or congenital heart disease [6].

In the USA, 2 million children require medical care for RSV annually [7]. This includes 1.7 million office visits [8], 180,000 emergency room (ER) visits for infants aged <1 year [9], and 400,000 ER visits for children <5 years old [8]. Between 60,000 and 144,000 infants are hospitalized annually because of RSV [3,5,9,10]; over half of these are <6 months old [8]. The average length of stay is 3.4–3.9 days [8,9].

The American Academy of Pediatrics recommends that infants at particularly high risk of severe RSV disease receive prophylaxis, eg administration of palivizumab (approved in 1998 in the USA) [11]. There are currently no approved vaccines to prevent RSV disease. Three vaccine candidates are in Phase I or II development [12]: MEDI-559 and MEDI-534 (MedImmune) and one from Novavax. To date, only seroconversion data have been reported for these vaccines [13,14]. The vaccination of pregnant women is a potential way to protect full-term infants from

RSV disease during the first few months following birth, based on antibodies passed transplacentally late in pregnancy [15]. In July 2012, Novavax announced partnership with PATH to fund clinical trials of its RSV vaccine candidate for immunization of pregnant women [16].

The literature evaluating the impact of an RSV vaccine is limited and no article has modeled the impact of RSV vaccination of children in the USA [17-20]. In this article, we developed a decision-analysis model to compare the impact of a hypothetical RSV vaccine for children at low and high risk of respiratory sequelae in the USA with the current standard of care (palivizumab prophylaxis for children at high risk). In addition, this article provides strategic information for policy-makers and vaccine manufacturers. In particular, our model aims to identify the critical endpoints that determine a vaccine's value.

Methods

Model

The monthly costs and outcomes of RSV disease were estimated for a hypothetical infant cohort from birth until a defined time point. Vaccination and no-vaccination scenarios were analyzed (Figure 1). For each scenario, the number of events (e.g. hospitalizations, death) attributed to RSV was calculated based on information from the literature and vaccine assumptions. The model's time horizon was 5 years after birth for healthcare utilization (as 98% of pediatric RSV-related hospitalizations occur during this period [8]), 10 years for the impact on asthma, and lifetime for loss of productivity due to premature death. The cohort size (4.23 million) was calculated using the average cohort size for 2007, 2008 and 2009 [21-23].

Two perspectives can be taken to analyze the vaccination program. In the analysis conducted from the healthcare system perspective, only direct medical costs are included. For the societal perspective, direct nonmedical costs (travel, meals, and lodging) and productivity losses are also included. More specifically, the incremental cost effectiveness ratio (ICER) from the societal perspective was calculated using the formula:

$ICER=[Co*Ra*(Pc+Ad)-Ms-NMs-Ps]/Qg$

where *Co* is the cohort size, *Ra* the vaccination rate, *Pc* the price per course, *Ad* the administration fees per course, *Ms* the medical cost savings from vaccination, *NMs* the direct nonmedical costs, *Ps* the productivity savings from vaccination (if societal perspective is taken), and *Qg* the number of QALYs gained from vaccination. Rotarix® price per course was used for *Pc* (see sensitivity analysis). A vaccination rate of 69% was assumed (see supplementary material). Note that no wastage and no advertising or adverse-event costs were assumed.

It is unknown whether an RSV vaccine would be administered to pregnant women or to infants. However, the model can be used to provide insight into both vaccination strategies by adjusting the onset and the duration of protection (see Discussion).

Medical Assumptions

Vaccine Efficacy and Safety

Because no efficacy data are available for any vaccines in development, the base case assumed that vaccination would reduce the probability of RSV-associated events by 50%. Equal effectiveness against RSV subgroups A and B was assumed. The start of protective immunity from the RSV vaccination is also unknown. The base case assumed a vaccination and a protective effect at birth. An exponential distribution was assumed for the duration of protection. The base case assumed a half-life of 12 months, which is lower than that for vaccines with known low persistence (eg, meningococcal, pertussis) [26,27]. The vaccine was assumed not to increase the incidence of medically attended events.

Resource Utilization

Table 1 shows key assumptions for healthcare utilization due to RSV. Data from Paramore et al [8] were used to estimate the risk by age of inpatient hospitalization and of hospital outpatient visits due to RSV infection. The age distribution of hospital outpatient visits was assumed to be similar to that of inpatient hospitalization. The risk by age of visits to the ER and to physicians' offices was based on data from Hall et al [28].

Mortality

Published estimates of RSV-associated deaths in the USA range from 130 to 390 annually for infants <1 year old (mortality rate range, 3.1–9.4 per 100,000), and reach 510 for children <5 years old [9,29,30]. The model used estimates of 5.4/100,000 for children <1 year old and 0.9/100,000 for children aged <5 years [29].

Increased Risk of Asthma/Wheezing

The average prevalence of asthma used in the model was 6% for children <5 years old and 10.5% for those aged 5–11 years [31]. Severe RSV disease in the first year of life was assumed to increase the risk of asthma/wheezing with a pooled odds ratio of 3.84 (95% CI: 3.23–4.58) [32]. Several studies have shown that the association between RSV and asthma decreases with age in children [33-35], and no higher prevalence of asthma was assumed once children reached 10 years old.

Quality of Life

The assumptions made of QALYs lost as a result of RSV disease are summarized in Table 2. The QALYs lost due to premature death were calculated by using the average utility value per age group and life expectancy [36,37]. The utility value is 0.03 lower for individuals with asthma compared with healthy people [38].

It was assumed that visits to pediatrician and hospital outpatient settings were associated with Lee's definition of mild cough [39]. ER visits and inpatient stays were assumed to be triggered by severe cough and by respiratory complications, respectively. Episodes of RSV infection were assumed to last 10 days [40], with a resulting loss in utility value of 0.005–0.010 per attack. More details regarding the QALY calculations can be found in the supplemental materials. After

an ER visit, the probability of being admitted to hospital or of making an office visit was assumed to be 29% and 30%, respectively [9].

Cost Assumptions

Cost estimates (Table 2) were derived from published sources and adjusted to 2011 US dollars, based on the Consumer Price Index (CPI) [46]. Costs rather than charges were used to better reflect the opportunity cost to society [47].

Medical Costs

Hospitalization costs for RSV were assessed using International Classification of Diseases, Ninth revision codes 079.6 (RSV), 466.11 (acute bronchiolitis due to RSV), and 480.1 (pneumonia due to RSV) for the principal diagnosis.

Administration Fees and Base-Case Price

Rotarix cost of vaccination (ie, vaccine price and administration fees) was used in the base case. Rotarix price per dose for the Centers for Disease Control and Prevention is $90.27; the private sector price is $105.8 (excluding excise tax) [48]. Private insurers and public payors, eg Medicaid, were assumed to pay physicians $25 and $11 per injection, respectively [49,50]. Access to public immunization programs, eg the Vaccines for Children Program, was assumed [51]. The mix between private (50%) and public payors/uninsured (50%) reflected infant coverage under 3 years old [52], resulting in an average fee of $18/dose (Table 2). Rotarix is administered as a two-dose series [53]; a cost of $232 per course was used in the base case. The cost of a new visit was not included in the model since it was assumed that the vaccine would be administered during an already planned visit (to an obstetrician/gynecologist for in-pregnancy

visit, or to a pediatrician for infant vaccination). In the US, infant vaccination takes place at birth and month 1 (hepatitis B), and at months 2, 4 or 6 (e.g. diphtheria, tetanus, acellular pertussis) [25].

Vaccination Program

Vaccination costs were calculated by multiplying the cohort size, coverage rate, number of doses per individual, and the vaccine's costs (including administration fees).

Direct Non-Medical cost

This cost was an average of that estimated to be incurred by parents of full-term ($278) and preterm ($389) infants for travel, meals, additional childcare, and other out-of-pocket expenses associated with hospitalization [43], adjusted to 2011 US dollars using the CPI [46] (Table 2).

Income Loss

Income was lost by: (i) parents who missed work to stay with sick children, either in hospital or in a physician's office; and (ii) infants who lost future income because they died prematurely of RSV.

One parent was assumed to lose 8 h of work per day of RSV hospitalization [44]. With an estimated average length of stay of 3.4 days [8], we assumed a total of 27 h lost work. To our knowledge, no analysis has assessed the loss of income due to RSV disease that did not require hospitalization. Therefore estimates from studies of rotavirus were used: 1.3 days of work were assumed to be lost for each episode treated in outpatient settings [45]. The cost of lost work (Table 2) was estimated using data from the 2010 National Compensation Survey [54].

The lost income from a premature death was calculated by multiplying the average income of individuals aged >15 years (2008-2010) and their expected life expectancy [37,55,56], leading to a lifetime lost income of $1.640 million per premature death ($481,000 if discounted to the time of birth; Table 2).

Discounting

The present value of future costs and benefits was calculated using a discount rate of 3%, as for the evaluation of meningococcal vaccination [57].

Sensitivity Analysis

As the effectiveness of an RSV vaccine is currently unknown, the values for efficacy, start and duration of protection were varied over a wide range in univariate sensitivity analyses. The impact of varying the mortality rate was also assessed. Finally, the impact of not assuming a causal link between RSV and asthma was estimated.

A probabilistic sensitivity analysis using a Monte Carlo simulation was also conducted using the distribution of key variables (Table 2). If no standard errors were provided for the mean estimate, a standard error equal to the mean was assumed. Since there is no known distribution around an RSV vaccine's characteristics, these were not included in the simulations. Therefore, the uncertainty estimates are only applicable to the vaccine's base-case scenario.

Results

Health and Cost Effect

Without vaccination, RSV infections in children were modeled to cause 95,800 inpatient hospitalizations, 537,400 ER visits, 1.66 million pediatrician office visits, and 381 deaths annually. Three-quarters (77%) of hospitalizations occurred in children <12 months old and 57% in children <6 months old. The death toll represented 29,375 life-years lost. The total number of QALYs lost per year was 41,900, driven by death (24,525 QALYs), utility loss due to RSV (13,850 QALYs), and excess asthma sequelae (3,550 QALYs). The annual medical cost was estimated at $1.15 billion; the main cost driver being inpatient costs ($530 million), followed by physician's office visits ($220 million), ER visits ($215 million), increased asthma sequelae ($135 million), and hospital outpatient visits ($55 million). Lost income and other expenses for caregivers was estimated at $625 million annually. Between 95,000 and 140,000 infants were estimated to have also received palivizumab prophylaxis in a given year [58-60].

Table 3 summarizes the modeled impact of the vaccination program with an efficacy of 50%, a half-life of 12 months and a vaccination rate of 69%: use of the theoretical vaccine avoided 66 deaths and 23,069 hospitalizations, and saved 2,047 life-years and 4,735 QALYs per vaccinated cohort (discounted values). The number of hospitalizations decreased by 25% and direct medical costs by 22%. The number of hospitalizations for infants <1 year decreased by 29%.

Using Rotarix pricing, RSV vaccination costs were $678 million (ie, $573 million in vaccine costs and $106 million in administrative fees). Accounting for the reduction of $236 million in direct medical costs, the net cost of vaccination was $443 million per vaccinated cohort. Therefore, the net cost per life-year saved would be $216,120, the cost per hospitalization

averted would be $19,172 and the cost per QALY gained $93,401 (healthcare system perspective). Income and productivity losses would decrease by $134 million. From the societal perspective, the cost per QALY gained would be $65,115.

Key Drivers of the Program

The vaccine can improve quality of life, decrease medical costs and productivity losses, and save lives. The relative contribution of each factor can be calculated by dividing by ($\lambda.Qg+Ms+Ps$), where λ is the willingness to pay for 1 QALY gained. There is no official λ in the USA. However, an intervention is usually seen as cost-effective if the cost per QALY gained is below $50,000 and not cost effective if the cost per QALY gained exceeds $100,000 [61]. Figure 2 shows the relative contribution of each driver assuming that λ=$100,000.

The greatest value drivers were the reduction in the number of children with RSV disease requiring medical care (25% of the overall number in the base case); QALYs gained from death avoided (21%); and the reduction in inpatient costs (15% of overall value). The impact of reducing the costs of ER and office/hospital outpatient visits had a relatively small impact on value (~4% and 5%, respectively). Income and productivity losses (ie, societal perspective) contributed 16%. Most of the societal impact was driven by savings regarding income loss by caregivers (11% of overall impact/dose). Overall, 56% of the value came from QALYs gained and 44% from cost reduction. If λ=$50,000, 39% of the value came from QALYs gained and 61% from cost reduction.

Sensitivity Analyses

Figure 3 (supplementary material) shows the impact on cost-effectiveness of modifying vaccine effectiveness and price. Using Rotarix pricing, the vaccine would be cost saving if the

effectiveness was above 75%. The month of onset of protective immunity had a great influence on the vaccine's impact (Figure 4, supplementary material). The cost-effectiveness ratio of a vaccine with 50% effectiveness that confers protection starting in the sixth month of life is $88,950 higher than one with protective immunity starting at birth. This result was expected because 57% of hospitalizations occur in children <6 months old. Similarly, a long duration of protection dramatically increased the value of the vaccine, especially if the vaccine's effectiveness was low (Figure 5, supplementary material). Increasing the half-life from 3 to 6 months had the most impact. The differences in cost-effectiveness between half lives of 18, 24, and 36 months were relatively small. With a high estimated mortality rate for infants >1 year old (9.4 rather than 5.4 per 100,000), the cost per QALY gained was $49,008 (societal perspective). With a mortality rate of 3.1 per 100,000, the cost per QALY gained was $78,415. If the link between asthma and RSV was assumed not to be causal, the cost per QALY gained was $88,513. There is some debate regarding whether productivity costs and health state valuation can be used in combination [62]. The impact of not including lost income due to premature deaths is limited; the cost per QALY gained increases to $71,984.

For all simulations, the incremental costs remained below $422 million (Figure 6a, supplementary material) and the cost per QALY gained remained below $107,000 (Figure 6b, supplementary material).

Discussion

On the basis of our model, an RSV vaccine would save lives, improve quality of life by reducing the number of weeks with cough and asthma, and reduce costs even if the effectiveness of the vaccine is only 50% at birth. Given the reduction in the disease burden and the annual sales potential in the USA, a vaccine against RSV should both provide substantial public health benefits and be economically viable.

The cost per QALY gained remained below $100,000 for 99% of the simulations (societal perspective). In 11% of the simulations, the cost per QALY gained was below $50,000. As previously described in the Sensitivity Analysis section, the estimates were obtained from simulations based on the distributions of RSV epidemiology and cost parameters. Additional parameters that are uncertain (vaccine effectiveness, the duration of protection, the start of protective immunity, and the causal link between RSV infections and subsequent asthma) were not varied in the Monte Carlo simulations.

The reductions in disutility from RSV disease, death, inpatient costs, and lost productivity represented 75% of the value of the vaccine. However, demonstrating a reduction in mortality is challenging given the low mortality rate. If the link between the reductions in hospitalizations and mortality is not accepted, vaccine manufacturers will have to identify acceptable surrogates for the reduction in mortality (eg, severe respiratory infections, days spent on ventilator). Reductions in RSV-like disease rather than RSV are more likely to be captured in physicians' settings given the lack of systematic diagnosis.

A number of assumptions in the model were conservative. For instance, we estimated a total of 27 h lost work, but the self-reported assessments of Leader et al included lost hours of up to five

adults (241 h) [43]. Furthermore, as there has been no analysis of the loss of income due to RSV disease in the outpatient setting, we used estimates from studies of rotavirus, but rotavirus symptoms are of shorter duration than those of RSV (3–8 days vs 1–2 weeks) [40,63]. In both these cases, the model's estimate of the benefits of an RSV vaccination program is probably conservative.

As previously mentioned, it is unknown whether an RSV vaccine would be administered to pregnant women or to infants. Table 4 can be used to compare the cost-effectiveness of maternal vaccination and infant vaccination. With maternal vaccination, the half-life of protective immunity will likely be short because the half-life of RSV maternal antibodies is 4–12 weeks [64-66]. The onset of protective immunity of maternal immunization will start at birth. Therefore, the ICER of maternal immunization could exceed $216,700 per QALY if the price per course is similar to that of Rotarix (Table 4). The base case assumes that the first dose of active immunization of infants is given at birth with protective immunity also starting at birth. However, if protective immunity starts a few weeks after the vaccination, the base case ICER would increase from $65,115 to $78,589 per QALY (Table 4). Based on the current vaccination schedule, a first dose could be given at 8 weeks (with the start of protective immunity at months 2 or 3). Infant immunization may give a longer duration of protection than maternal vaccination depending on the number of administered doses. A 4-dose series (e.g. at 2, 4, 6 and 12 months) may provide a half-life duration of protection exceeding 18 months (i.e. with an ICER below $68,720) [26,27].".

In Europe and in regions of North America with well-defined seasons, outbreaks typically occur between November and April, with a peak in January and February [67]. If the vaccine has a short duration (less than 6 months), seasonal vaccination could be considered (see the analyses

by Bos et al. (2007) [17] and Meijboom et al. (2012) [19]). Seasonal vaccination will increase the cost-effectiveness of the vaccine (i.e. the ICER of a seasonal vaccination will be lower than a full-year vaccination).

The vaccination program did not assume a reduction in the utilization of palivizumab for children at high risk (including premature infants). In other words, it was assumed that at-risk children would receive palivizumab even if they were vaccinated. This conservative assumption was motivated by the fact that the protection of infants at birth may not be sufficient to justify discontinuing the palivizumab prophylaxis program. More specifically, infant vaccination would require weeks for onset of protective immunity and premature infants receive lower levels of passive immunization from maternal vaccination [68]. To refine this assumption, the impact of the vaccine for infants receiving palivizumab should be gathered during clinical trials. Alternatively, the impact of palivizumab for vaccinated, at-risk children could be measured.

The analysis assumed a causal link between RSV infections and subsequent asthma, which is controversial but is supported by a recent study [69]. If the issue remains contentious before Phase III trials begin, the incremental clinical costs to prove a reduction in asthma should be weighed against the impact on price.

Meijboom et al (2012) showed that infant vaccination against RSV could be cost-effective in the Netherlands with a price of €127.50 per course and a vaccine efficacy of 30%, 60%, and 75% at age 0, 1 and 3 months, respectively [19]. Assumptions of inpatient hospitalizations (900 per 100,000 infants <12 months old) and excess mortality (2.5 per 100,000 infants <12 months old) were more conservative than in our model. Acedo and colleagues (2010) developed a dynamic model (age-structured SIRS model) and found that a vaccine with 100% efficacy could be cost

saving at a cost of €300 per course [20]. Since the model takes into account indirect transmission, the results are more favorable than those in this article.

Limitations

The true value of the vaccine could be underestimated as not all potential benefits were modeled: (i) humans are the only reservoir of RSV and vaccination could lead to herd immunity, which was not assessed by our static model; (ii) the QALYs lost by primary caregivers of infected children were not included in the evaluation and proved substantial for rotavirus [70]; and (iii) income and disutility loss were not assessed for RSV infections that only required home care. The value of the vaccine was also overestimated if an increase occurs in the incidence of medically-attended events due to vaccination, as this was not taken into account. Additional limitations can be found in the Supplementary Material.

Conclusions

Immunization against RSV could reduce the burden of RSV infection if we assume a vaccine with 50% efficacy combined with fast waning of protection. The cost-effectiveness criteria in our model suggest that an RSV vaccination program would be at least as important as immunization against rotavirus. The key value drivers for society are reductions in: (i) disutility associated with RSV disease; (ii) mortality; (iii) inpatient costs; (iv) asthma sequelae and costs; and (v) lost workdays by caregivers. Reduction in mortality may be difficult to prove in clinical trials, and relevant surrogates may be needed.

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Figures

Figure 1. Model structure.

[a]Healthcare utilization includes physician, hospital outpatient and emergency room visits, and/or inpatient hospitalization.

ER indicates emergency room; RSV, respiratory syncytial virus.

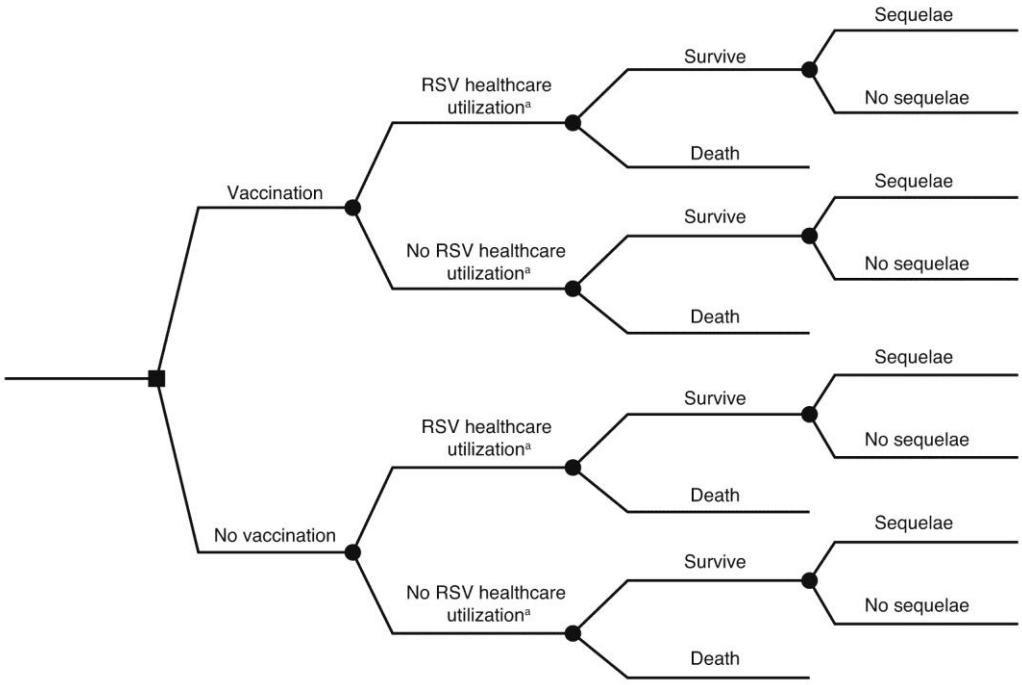

Figure 2. Drivers of the economic value of the vaccine.

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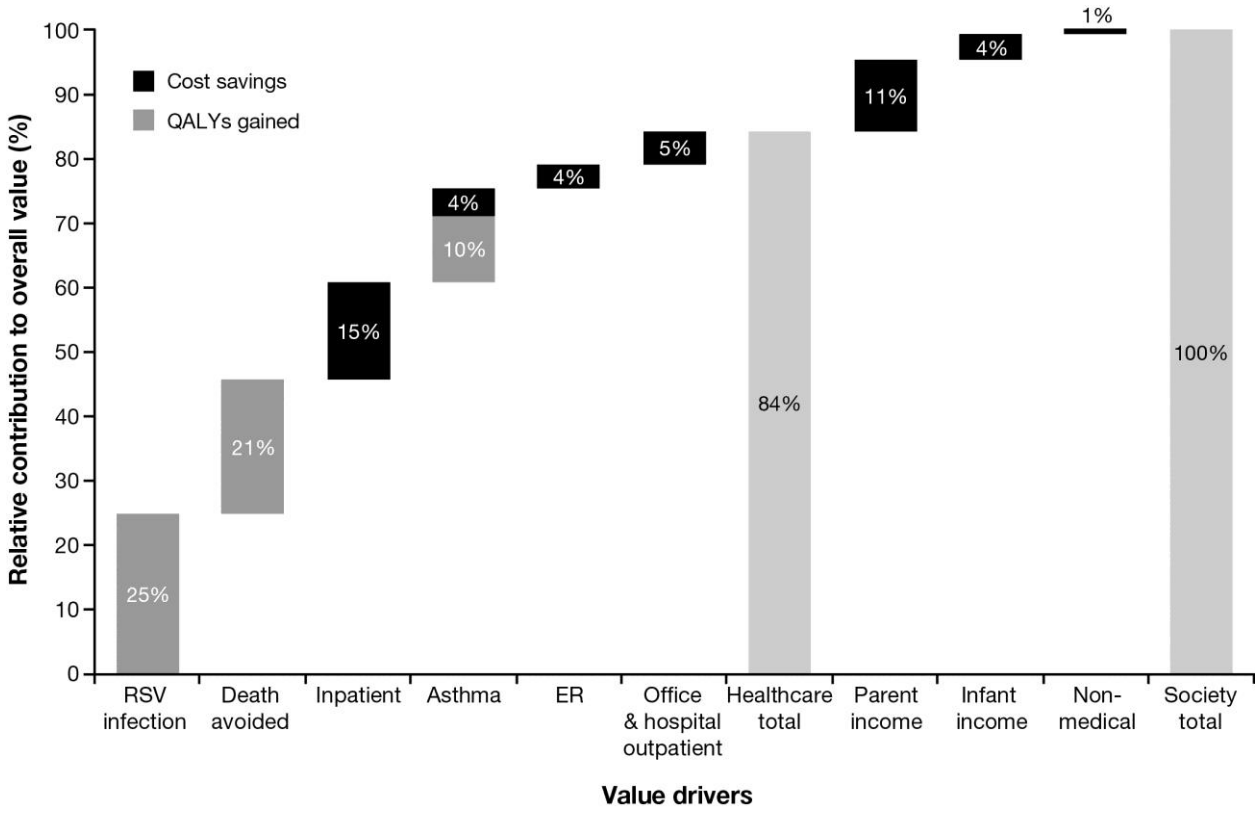
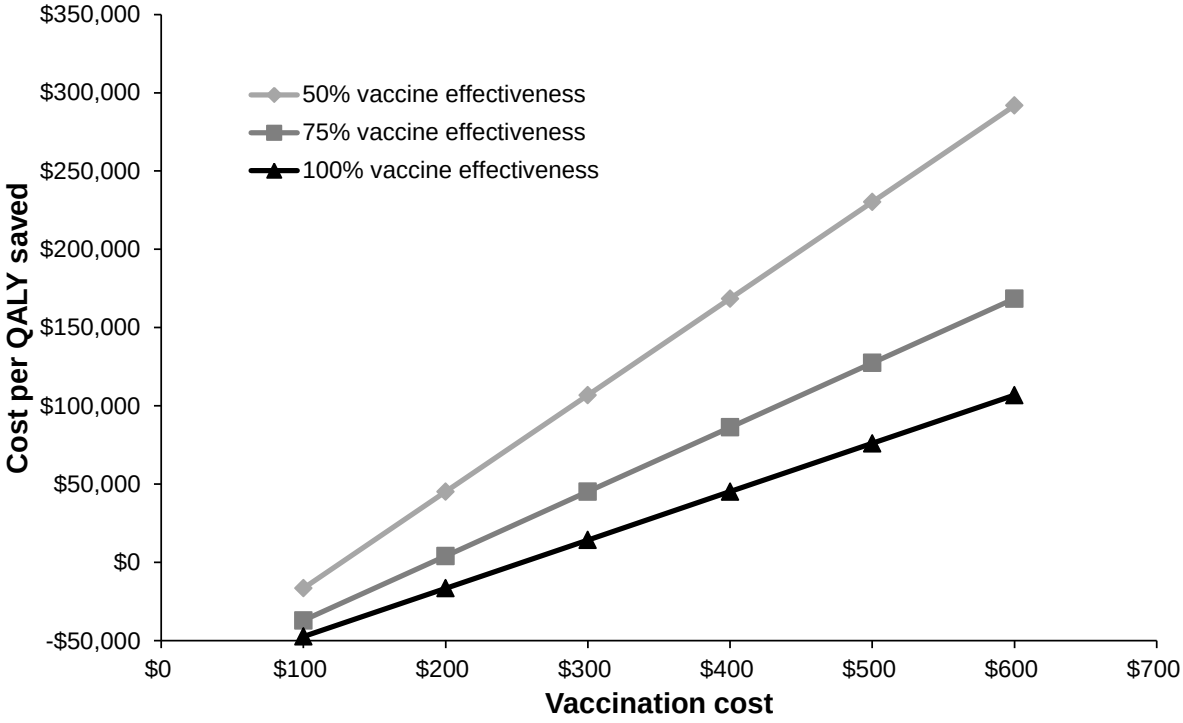


Total values are shown from healthcare provider and societal perspectives.

ER indicates emergency room; RSV, respiratory syncytial virus; QALY, quality-adjusted life-year.

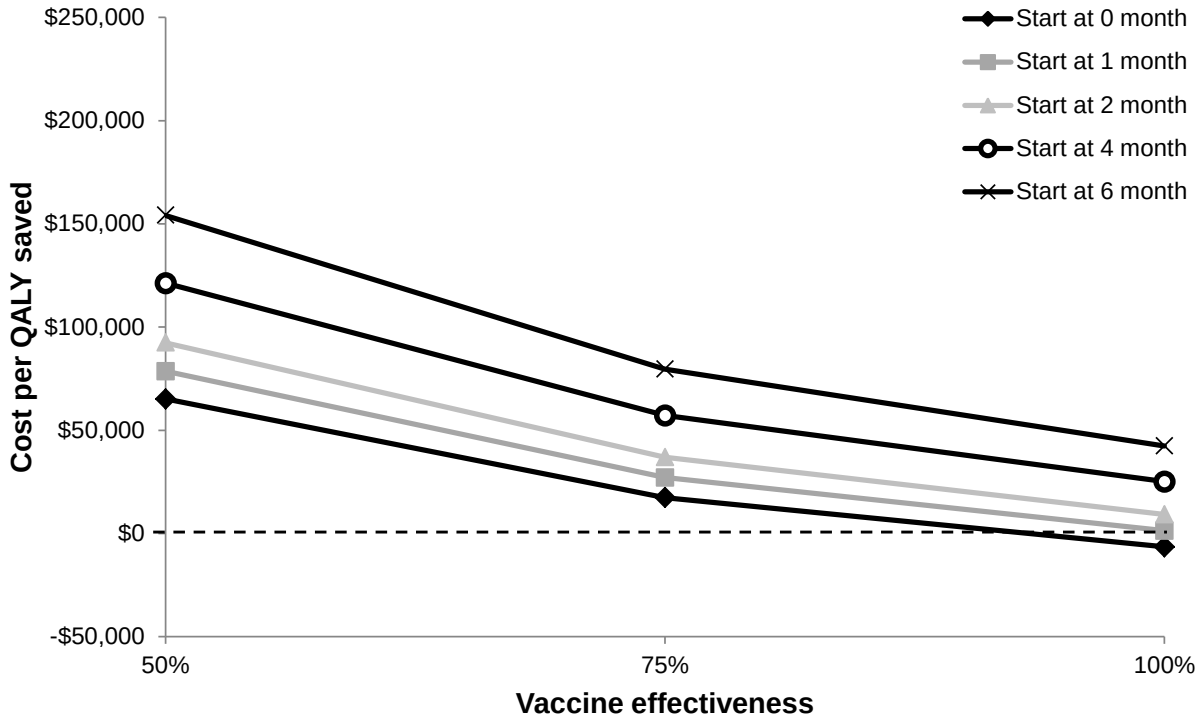
Figure 3. Impact of vaccine effectiveness and vaccination cost on the cost-effectiveness of a hypothetical respiratory syncytial virus vaccine.



Vaccination cost is the vaccine price and administration fees per vaccinated infant.

QALY indicates quality-adjusted life-year.

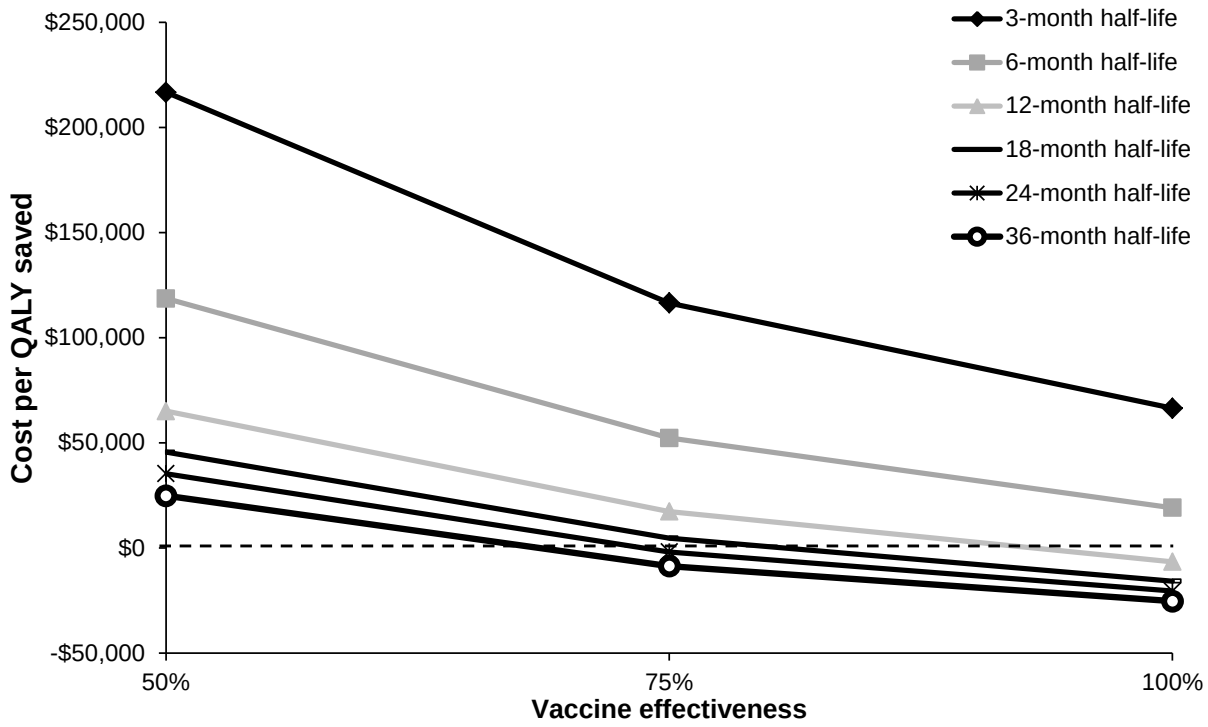
Figure 4. Impact of vaccine effectiveness and the month in which protection is started on cost-effectiveness.



Each line represents different months of onset of protective immunity.

QALY indicates quality-adjusted life-year.

Figure 5. Impact of vaccine effectiveness and half-life of protection on cost-effectiveness.

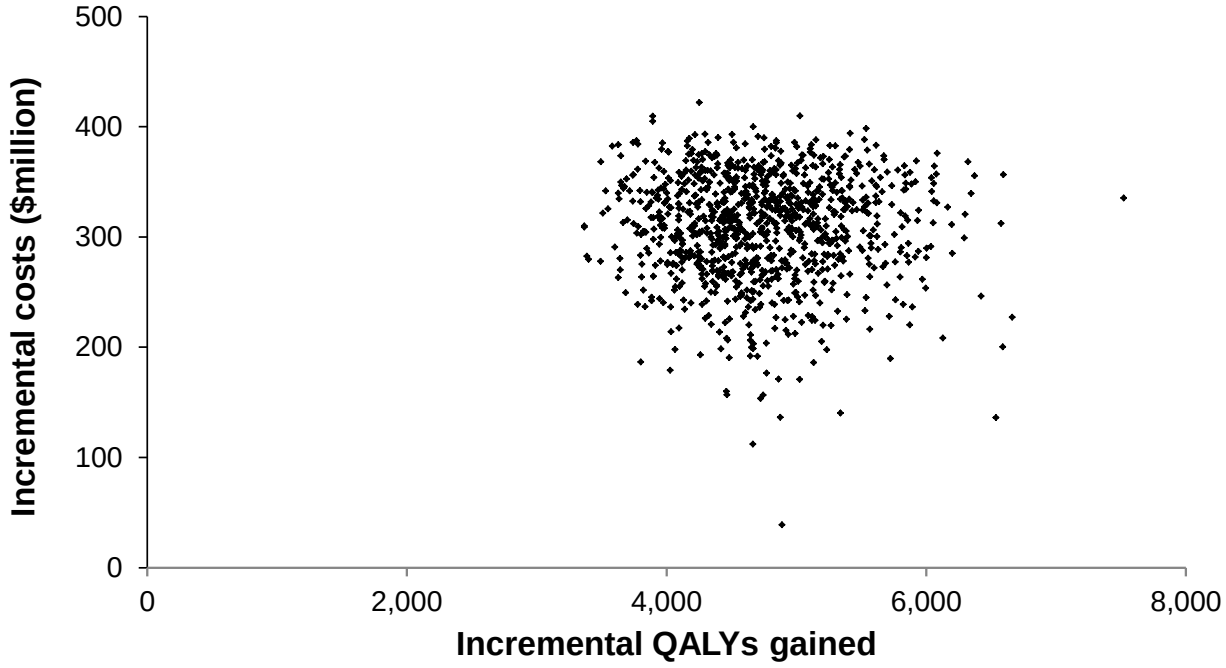


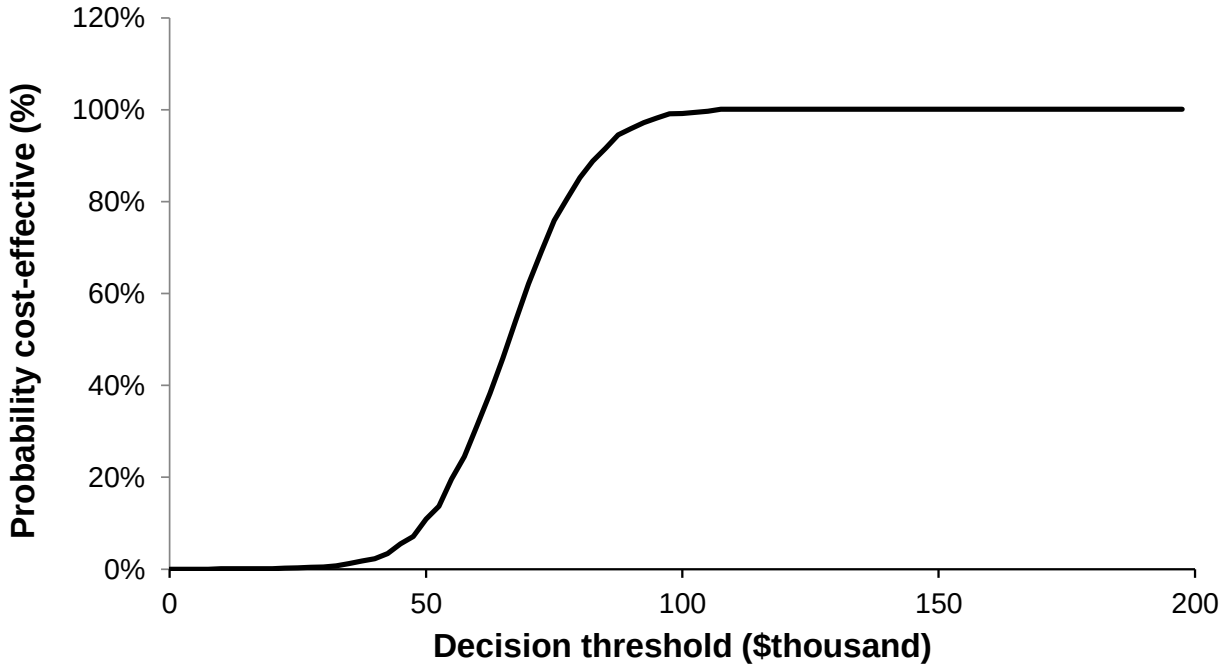
Each line represents different durations of half-life of protection.

QALY indicates quality-adjusted life-year.

Figure 6. Monte Carlo simulation results based on probabilistic sensitivity analysis (1,000 simulations).

(a) cost-effectiveness and (b) cost-effectiveness acceptability curve for respiratory syncytial virus immunization





QALY indicates quality-adjusted life-year. Each dot represents the outcome of one simulation.

Table 1. Impact of Respiratory Syncytial Virus Disease on Healthcare Utilization (Premature and Full-Term Infants Combined)

	Incidence per 1,000 Population				Mortality Rate
Age at Time of Infection	**Hospitalization**	**ER Visits**	**Hospital Outpatient**	**PCP Visits**	**(per 100,000)**
0–2 months	32.0	55	88.6	132	5.4
3–5 months	19.3	55	53.3	132	5.4
6–8 months	11.5	57	31.8	177	5.4
9–11 months	6.7	57	18.6	177	5.4
12–23 months	2.4	32	6.7	66	0.9
24–35 months	2.4	13	6.7	57	0.9
3–4 years	0.2	13	0.5	57	0.9

Abbreviations: ER, emergency room; PCP, primary care physician (includes pediatrician).

Table 2. Distributions Used in Probabilistic Sensitivity Analysis (Monte Carlo Simulation)

Category	Variable	Distribution	Mean (SD)	Source
Asthma	Incidence (general population)	Beta	0–4 years: 6.0% (0.54%) 5–11 years: 10.5% (0.56%)	Bloom et al. [31]
	Increased risk of asthma (OR)	Log-normal	3.84 (0.34)	Regnier & Huels [32]
	Asthma	Beta	0.03 (0.01)	Gold et al [38]
Hospitalization	Hospitalization rate (per 1,000 population)	Beta	From 32.0 (0.2) for 0–2 months to 0.2 (0.0) for 3–4 years	[8], [28]
QALY lost per	1 event with hospitalization	Beta	0.010 (0.006)	[39], [40]
event	1 event with severe cough	Beta	0.008 (0.004)	[39], [40]

	1 event with mild cough	Beta	0.005 (0.002)	[39], [40]
Mortality	Rate (per 100,000) age <12 months	Beta	5.4 (0.4)	[29]
	Average QALYs lost/year (0–20 years)	Beta	0.87 (0.02)	[36], [37]
	Average QALYs lost/year (21–50 years)	Beta	0.86 (0.01)	[36], [37]
	Average QALYs lost/year (51–70 years)	Beta	0.80 (0.01)	[36], [37]
	Average QALYs lost/year (>20 years)	Beta	0.74 (0.02)	[36], [37]
Costs/unit	Inpatient hospitalization	Gamma	$5,550 ($216)	HCUP KID [41]
	ER visit	Gamma	$395 ($395)	Paramore et al [8]
	Outpatient visit	Gamma	$209 ($209)	Paramore et al [8]

	Pediatrician consultation	Gamma	$131 ($131)	Paramore et al [8]
	Annual cost of asthma per reported person[a]	Gamma	$1,145 ($372)	Kamble & Bharma [42]
	Average administration fee per vaccine dose	Fixed	$18	See text
Societal/unit	Direct non-medical costs per hospitalization	Gamma	$310 ($237)	Leader et al [43]
	Parents' lost income per hospitalization	Gamma	$579 ($11)	[44], [54]
	Parents' lost income per attack seen in outpatient settings	Gamma	$221 ($43)	[45], [54]
	Lifetime income lost by an infant who died of RSV (discounted)	Fixed	$481,000	See text
Treatment	Probability of inpatient treatment after	Fixed	29%	Leader & Kohlhase [9]

	making an ER visit			
pathway	Probability of making a physician office visit after an ER visit	Fixed	30%	Leader & Kohlhase [9]

Abbreviations: ER, emergency room; HCUP KID, Healthcare Cost & Utilization Project Kids' Inpatient Database; HRQoL, health-related quality of life; OR, odds ratio; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus; SD, standard deviation.

[a]Costs of asthma and wheezing assumed to be the same.

Table 3. Impact of Vaccinating One Cohort (4.2 Million Live Births)[a].

	Hospitalizations Avoided[b]	Deaths Avoided	Life-Years Saved	QALYs gained
Total	23,069 (22,501–23,593)	66 (59–75)	2,047 (1,817–2,302)	4,735 (3,698–6,037)

[a]All results were calculated assuming a discount rate of 3%. [b]Values are rounded to the nearest whole number.

In parenthesis, 2.5th and 97.5th percentiles from probability sensitivity analysis.

Table 4. Discounted Cost ('000 $) per Quality-Adjusted Life-Year Gained, as a Function of Month of Onset of Protective Immunity and Half-Life Duration of Protection (Societal Perspective)

	Month of Onset of Protective Immunity				
Half-Life Duration of Protection (months)	**0**	**1**	**2**	**4**	**6**
3	216.7 (169.2–274.2)	243.0 (191.4–307.3)	268.7 (213.5–341.5)	318.4 (251.4–407.0)	369.0 (282.1–477.4)
6	118.7 (88.8–153.3)	137.0 (101.3–178.4)	155.6 (114.4–199.6)	194.2 (149.3–251.1)	238.0 (181.2–311.0)
12	65.1 (41.0–93.7)	78.6 (49.5–110.0)	92.3 (59.6–127.2)	121.3 (84.3–162.0)	154.1 (108.3–212.3)
18	45.6 (17.1–68.1)	57.0 (28.4–82.6)	68.7 (38.5–99.7)	93.2 (61.1–131.8)	120.6 (78.3–171.2)
24	35.3 (9.2–56.9)	45.7 (16.3–70.7)	56.3 (28.1–84.6)	78.3 (46.4–115.5)	102.7 (66.5–146.9)

36	24.8 (–1.3–45.3)	34.1 (4.4–57.0)	43.4 (15.0–67.8)	62.9 (33.9–96.6)	84.2 (50.8–127.0)

Base case highlighted in gray. In parenthesis, 2.5th and 97.5th percentiles from probability sensitivity analysis

Appendix

Coverage Assumptions

It is currently unknown whether an approved RSV vaccine would be administered to pregnant women or to infants. The only routine vaccinations currently recommended in the USA for pregnant women are influenza and tetanus-diphtheria, if the woman has not received tetanus-diphtheria vaccination within the last 10 years. The average influenza vaccination rate was 49% in pregnant women in 2010 [24]. Vaccination coverage in 2011 for routine infant immunization was 69% for hepatitis B at birth. It was between 84% (first dose of pneumococcal conjugate vaccine) and 87% (first dose of diphtheria, tetanus, and pertussis triple vaccine) at age 3 months [25]. A vaccination rate of 69% was assumed in the base case (vaccination and protective effect at birth). A vaccination rate of 85% or higher was assumed for scenarios where the start of protective immunity is ≥3 months. A vaccination rate of 49% was assumed for maternal immunization.

As no impact on herd immunity and no fixed costs are included, the coverage assumptions would not impact the cost-effectiveness of the vaccine.

Quality of life

The number of QALYs lost due to premature death was calculated from the number of years lost with average utility values of 0.87 between birth and 19 years of age, 0.86 between 20 and 49 years, 0.80 between 50 and 69 years, and 0.74 between 70 years and expected age of death

(77.90 years) [36-37]. Therefore, a death in the first year of life results in a QALY loss of 65.1 (undiscounted) and 26.4 (discounted) (Table 5).

The value for QALYs lost due to asthma (0.03) was based on a version of the Health Utility Index (HUI) constructed from questions from the National Health and Examination Survey I Epidemiologic Follow-up Study (NHFES) [38]. In that survey, the mean HUI score was 0.78. The value of 0.03 for asthma represented the adjusted effect of asthma on the Constructed Health Utility Index.

It was assumed that visits to pediatrician and hospital outpatient settings were associated with mild cough as defined by Lee and colleagues [39]. ER visits and inpatient stays were assumed to be triggered by severe cough and by respiratory complications, respectively. For mild cough, severe cough, and respiratory complications, Lee and colleagues (2005) estimated utilities of 0.78, 0.67 and 0.58, respectively, by using short-term time trade-off. The QALY loss for each event was calculated assuming that RSV infections last 10 days [40], with a resulting loss in utility value of 0.005–0.010 per attack (Table 6).

Potential Additional Limitations

It was assumed that no increase in RSV disease would occur after the efficacy of the vaccine wanes, as the reduced severity of infection in older infants and children may be driven more by age (with the associated increase in airway diameter) than by natural immunity [71]. However, if partial immunity is driven by natural infection [72] the reduction of RSV disease was overestimated.

The incidence of hospitalization was obtained from data collected in 2000 [8]; the number of cases has been lower in recent years [41], which could negatively impact on the economic benefits of immunization.

Finally, RSV is a mutating virus with subgroup B evolving faster than subgroup A [73]. More specifically, the mutation rate for sub-group B is $3.5x10^{-3}$ (vs. $2.6x10^{-3}$ for subgroup A) changes per nucleotide per year [73]. If a vaccine has a long duration of protection (greater than 12 months), an implicit assumption is that the vaccine will offer protection for multiple seasons. If it is not the case, the cost-effectiveness is overstated in this model. However, the risk of over-estimation of effectiveness is limited. Vaccines based on RSV F protein nanoparticle (e.g. the candidate by Novavax), which does not vary between subgroups, are expected to protect well against both subgroups. Also, although there has been genetic change in RSV, there is no known antigenic drift [74].

Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis.

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Introduction

Respiratory syncytial virus (RSV) is a common and highly contagious cause of respiratory viral infection in infants and young children. Over two-thirds of infants in the USA are infected during their first RSV season, and virtually all children have been infected at least once by the time they reach their second birthday, with half having experienced two infections.[1] Only a small fraction (2–3%) present with severe symptoms and require hospitalization.[2] Some infants and young children are particularly at risk, including premature infants, children <2 years old with chronic lung disease or congenital heart disease, children living with a child <5 years old or attending childcare, infants with congenital abnormalities of the airways or neuromuscular disease, and those who are immunocompromised.[3] Pre-existing neuromuscular impairment has also been identified as a risk factor for severe RSV disease.[4] Furthermore, among infants hospitalized for RSV infection, pre-term infants with chronic lung disease face a higher risk of requiring mechanical ventilation.[5] Nosocomially acquired RSV infection also represents a greater risk factor for disease complications in hospitalized children with RSV infections than does RSV acquired in the community.[6]

Infants and children who have experienced severe RSV infections often develop respiratory sequelae, such as wheezing, asthma, variable airways obstruction, acute respiratory disease, hyperinflation, or allergy.[7] Some authors have suggested a causal link between RSV infection and asthma,[8,9] but this is controversial. Other researchers think that RSV does not cause asthma and assert that RSV infection and asthma are associated with the same underlying medical conditions.[10] The existence and the quantification of a relationship between RSV infections in

infancy and wheezing/asthma in later life may have important implications for the evaluation of new treatments against RSV infections. To our knowledge, no studies have been published that have combined systematic review and synthesis of the evidence. We therefore performed a meta-analysis of the existing evidence.

Methods

Study Selection

Our aim was to retrieve all relevant studies measuring the association between the incidence of asthma/wheezing and prior hospitalization due to RSV disease in the first 3 years of life. To achieve this objective we first identified all reviews (including systematic reviews) catalogued in the MEDLINE and EMBASE databases that had already addressed the same issue (Step 1), and then identified additional studies published after the selected reviews (Step 2). The detailed search strategies for these two steps are shown in the Supplemental Digital Content.

Articles identified in Steps 1 and 2 were selected for inclusion only if they met all the following criteria: (i) the objective of the article was to quantify the level of association between RSV infection and asthma/wheezing sequelae; (ii) the maximum age at the time of RSV infection was <3 years; (iii) a follow-up period was included; (iv) diagnosis of RSV infection was virologically confirmed in all cases; (v) either a control group including patients without hospitalization for respiratory disease was used or the study was a cohort study measuring inpatient hospitalization due to RSV; (vi) an outcome was measured; and (vii) articles were published within the last 35 years (i.e., post 1977). We excluded studies that assessed the impact of prophylaxis against RSV (prevention or control) and studies that focused on high-risk groups.

The inclusion criteria were defined before screening of the literature and two reviewers (SR and JH) independently assessed the eligibility of the reviews and studies. In the first step, all retrieved reviews were read. The articles identified in the second step were reviewed if the titles

and abstracts indicated potential relevancy. Discrepancies between reviewers were resolved by discussion.

Quality Assessment

The authors assessed the quality of the studies independently. A study was considered to be of high quality if blinding was adequate, the control groups contained no individuals with RSV infection, and confounding factors were properly captured or addressed. Blinding was considered adequate if the person making the diagnosis was not aware of a child's status for hospitalization in earlier life due to RSV disease. Appropriate confounding methodology had to report the value of relevant confounders and adjust odds ratios if the distribution of the confounding variable(s) was unbalanced between the index and control groups. Potential risk factors for the development of asthma, such as family history of asthma, gender, or parental smoking (current or during pregnancy), were considered to be the most relevant confounders.[3,11,12] More controversial risk factors, such as breastfeeding and gestational age at birth (or birth weight), were also included.[13-15] Parental socioeconomic status or educational levels also had to be reported but the presence of these variables was considered to be less important. Reporting of race was also considered to be a desirable factor in studies conducted in the USA.[3] Studies based on physician diagnosis were considered to be of higher quality than those relying on parental diagnosis. We did not distinguish between a physician's diagnosis retrieved from chart review and one reported by parents.

Meta-Analysis and Simulations

The odds ratios of respiratory sequelae occurring with and without prior RSV hospitalization were retrieved. For prospective birth cohort studies or studies with unbalanced index and control groups, odds ratios adjusted for risk factors were used.

The meta-analysis assumed a fixed-effects model (i.e., all studies were assumed to estimate a single value of impact). The calculations were performed using log odds ratios because these have an approximately normal distribution and can be used in the absence of raw data. The studies were weighted using the inverse variance method. The stability of the odds ratio estimate was tested by using sensitivity analyses in which the studies with the most weight were removed. The level of heterogeneity was estimated using the Higgins I^2 statistic, which measures the variation between study results due to heterogeneity and not chance.[16] Higgins I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively, between studies. If heterogeneity between studies was high or moderate, the results of a random-effects model were also reported, and stratified analyses were conducted to examine potential sources of heterogeneity. The predetermined subgroups were based on the disease definition (asthma/recurrent wheezing versus wheezing) and on quality characteristics, such as adequate blinding, appropriate treatment of confounding variables, physician diagnosis, and exclusion of RSV in control groups. A number of longitudinal studies[17-23] found that the association between RSV infection and asthma decreased as the children become older. Therefore, a meta-regression was used to assess whether age at follow-up affected the association between asthma and RSV.

Potential publication bias was evaluated by analyzing the symmetry of funnel plots, and by using Egger's test[24] to compare the effect of study sizes on the results.

Finally, the percentage of asthma cases associated with RSV infection in infancy was assessed to estimate the clinical relevance of the findings. The percentage of infants with RSV infection who developed asthma later in life was also estimated. To achieve this, the distributions of infants who had asthma with and without RSV disease in infancy were simulated using: (i) the prevalence of asthma in children <5 years old;[25] (ii) the odds ratio from the meta-analysis for children <5 years old; and (iii) the rate of hospitalization due to RSV disease in the first year of life.[26] A total of 20 000 simulations were used to create the distributions. The distributions and equations used in the simulations are provided in the Supplemental Digital Content.

Meta-analyses were performed using the Stata statistical analysis program (version 12.1; StataCorp LP, College Station, TX, USA). Simulations were run using the WinBUGS statistical program (version 1.4; MRC Biostatistics Unit, Cambridge, UK).

Results

Systematic Review

The algorithm for selecting reviews (Step 1) and additional studies published after the relevant systematic reviews (Step 2) can be accessed in the Supplemental Digital Content.

In Step 1 of our analysis, 21 unique reviews were retrieved, seven of which were deemed relevant[7,8,27–31] (Supplemental Digital Content); reasons for rejection of the other reviews are summarized in the figure. The paper by Perez-Yarza et al.[7] was a well-conducted systematic review, as the included studies were determined independently by the authors who also thoroughly assessed their quality. In addition, the review reported the detailed search strategy across the most relevant databases (Cochrane Plus Library, MEDLINE and EMBASE).

The seven selected reviews reported 38 pertinent articles for measuring the impact of the association between asthma and RSV. Eighteen papers were deemed relevant[17–23,45–55] and 20 articles were excluded (Supplemental Digital Content).

Articles assessed in Step 2 were limited to those published after October 2010 (the date of the last article in the selected reviews) and provided 54 abstracts. After reading these abstracts, the two independent evaluators selected seven articles that were retrieved and read in full, but only one article[76] was deemed relevant (Supplemental Digital Content).

By combining the articles from Steps 1 and 2, the meta-analysis included 19 articles representing 15 unique studies (Table 1). Six articles reported the results of two longitudinal studies at different follow-up ages.[17–22] In such cases, where a study had several periods of follow-up, we

used the values from the first follow-up that took place after 3 years of age in our analysis (Korppi et al.[22] and Sigurs et al.[20]). The studies by Pullan and Hey[46] and Sims et al.[48] were conducted in the same geographic region (Tyneside, UK) but examined individuals born in different years. Overall, 82 008 individuals contributed to our analysis. Of those individuals, 1533 experienced a virologically confirmed RSV hospitalization in the first 3 years of life. In 9 out of 15 studies, the average age at hospitalization was less than 6 months. In all but two studies, the hospitalization was reported to have occurred in the first year of life.

All studies except that reported by Juntti et al.[45] had either inappropriate blinding or did not report blinding methodologies. The exclusion of RSV cases from the control group was not always guaranteed: it is possible that cases of RSV were present in the control group in the studies reported by Korppi et al.[21] and Mikalsen et al.[76] Given the short duration of follow-up in the study by Schauer et al.[47] the infants with wheezing in the control groups could have had an RSV infection not requiring hospitalization. Therefore, the reported results may be related to RSV infection and not asthma.

Five studies were considered to have appropriate confounding methodologies for family history of asthma, gender, birth weight or gestational age, and parental smoking.[20,23,49–51] In three of these studies,[23,49,51] odds ratios were adjusted based on multiple confounders. In the other two,[20,50] the distribution of confounding variables was not significantly different between the RSV and control groups and, therefore, did not require adjustment of the odds ratios. The level of maternal education was only reported (and adjusted) by Stein et al.[23] and Henderson et al.[51] Stein et al.[23] and Escobar et al.[49] studied American children, but only Escobar et al.[49] adjusted results by race. All other articles were deemed to have inappropriate methods of addressing

confounding. Korppi et al.[22] and Mikalsen et al.[76] reported the distribution of no or only a few confounding factors. Mok and Simpson[52] and Murray et al.[53] did not report the distribution of risk factors for individuals who were RSV positive in the bronchiolitis index group. In the study by Osundwa et al.[54] only equal distribution of gender and history of atopy between RSV and control groups was reported. Sims et al.[48] and Pullan and Hey[46] did not report the family history of asthma. Studies by Pullan and Hey[46] Schauer et al.[47] and Juntti et al.[45] had an unequal distribution of confounders, with more risk factors in the RSV group than in the control group (parental smoking in the studies by Schauer et al.[47] and Pullan and Hey[46] family history of asthma in the study by Juntti et al.[45]), but did not adjust the odds ratios. For these studies, the association between RSV and asthma may be overestimated. Finally, in the study by Singleton et al.[55] odds ratios were only adjusted by one confounder at a time.

Outcomes of Interest for Meta-Analysis

The outcome of interest was recurrent wheezing or asthma in the 12-month period before the follow-up study. The medical definitions of asthma and wheezing varied slightly between studies. For example, wheezing was defined as a "whistling sound coming from the chest" by Sims et al.[48] and as bronchial obstruction by Sigurs et al.[19] and Schauer et al.[47] Wheezing was defined as recurrent if at least three episodes occurred in the year preceding the follow-up study. For Sigurs et al.[20] the difference between asthma and wheezing depended on whether or not the diagnosis was made by a physician.

If a study reported several potential outcomes of interest (e.g., asthma, wheezing, and recurrent wheezing), the selection of the outcome used in the meta-analysis was based on the following

criteria (sorted by descending level of importance): (i) diagnosis by a physician was preferred over parental assessment; (ii) current respiratory status or respiratory status in the last 12 months was selected over cumulative outcome (e.g., "asthma diagnosis at any time"); (iii) asthma was selected over wheezing.

Key information from the selected studies is summarized in Table 1, in particular, whether physicians or parents collected data on asthma or wheezing.

Meta-Analysis: Association of RSV With Asthma or Wheezing

Nine of the 15 studies reported a statistically significant association between hospitalization due to lower respiratory tract RSV infection in the first 3 years and asthma/wheezing later in life (Fig. 1). In the meta-analysis, RSV hospitalizations were associated with a significantly increased risk of wheeze/asthma (odds ratio: 3.84; 95% confidence interval [CI]: 3.23–4.58). The study by Escobar et al.[49] contributed 52% to the overall odds ratio. When this study was removed, the association remained strong with an odds ratio of 3.36 (95% CI: 2.61–4.31), which remains within the 95% CI of the principal analysis. Three studies[22,47,48] contributed less than 1% to the pooled result because of a high variance in the estimate of the log odds ratio. The high variance was mainly driven by a low number of asthma/wheezing cases in the control group. Higgins I^2 was 45%, indicating a moderate degree of heterogeneity between studies. Given the level of heterogeneity, an analysis was conducted using a random-effects model, which provided an odds ratio estimate of 3.63 (95% CI: 2.69–4.90) with a between-study variance (τ^2) of 0.13. As the funnel plot appeared to be symmetrical (Supplemental Digital Content) and the p-value from the Egger's test was 0.79, we conclude that there was no evidence of publication bias.

The association between RSV hospitalization and asthma/wheezing decreased with age at follow-up (Fig. 2). The log odds ratio between asthma and RSV hospitalization decreased by 0.11 ($p = 0.017$) for each additional year of follow-up, consistent with the findings from longitudinal studies by Sigurs et al.,[17–20] Korppi et al.,[21,22] and Stein et al.[23] When taking into account age at follow-up, heterogeneity between studies was low (residual $I^2 = 17\%$; between-study variance 0.02). Age at follow-up can explain more than 86% of the between-study variance. The meta-regressions showed that the results of two studies[48,50] were unexpected given their log odds ratios of 2.3 and 2.9, and age at follow-up of 8 and 7 years old, respectively. As mentioned above, the definition of respiratory sequelae varied between studies. The association in articles reporting asthma/recurrent wheezing was lower than for those reporting wheezing; however, the odds ratios were not significantly different ($p = 0.67$). Similarly, the association was not significantly different depending on whether or not the diagnosis was made exclusively by a physician ($p = 0.20$). Studies with appropriate confounding methodologies had reported higher odds ratios than those without and the difference was significant ($p = 0.02$). This result is surprising since, as discussed previously, some studies without appropriate confounding were likely to overestimate the association between RSV and asthma.

All stratified meta-analyses are summarized in Table 2. Based on the stratified analyses, a meta-regression was conducted using age of follow-up and confounding methodologies, but explained less heterogeneity than the meta-regression with age of follow-up only.

Simulation: Percentage of Asthma Cases Linked to RSV Infections

Based on the meta-analysis and the results of 20 000 simulations, on average 21.9% (95% CI: 9.5–37.8%) of children hospitalized because of RSV infection in their first year of life will develop asthma in the first 5 years of life.

Discussion

This study identified a number of publications that have investigated the potential association between hospitalizations for RSV and respiratory sequelae. Notably, there was some heterogeneity between the studies; however, this was substantially reduced when the age of follow-up was considered. Once the age of follow-up was taken into account, the meta-regression showed that the association between asthma and RSV hospitalization in the early years reduced over time. One explanation could be that both index and control groups had longer exposure to factors known to trigger the development of asthma (e.g. environmental tobacco smoke, house dust mite, damp indoor environments and mold etc.),[83] which could have confounded the association. Another explanation could be that some children with early onset of asthma get better with time, which would reduce the odds ratio over time.[84]

Implications: Percentage of Asthma Cases Linked to RSV Infections

According to Paramore et al.[26] 1.74% of children are hospitalized in their first year of life due to RSV infections, which amounts to 65 544 hospitalizations in the USA each year. The simulation using the results of the meta-analysis showed that, on average, 21.9% of these children will develop asthma in the first 5 years of life. These children are estimated to represent, on average, 6.4% (95% CI: 2.9–10.8%) of all asthma cases in children <5 years old. Therefore, if the association between asthma and RSV is causal as indicated by Wu and Hartert[8] and Simoes et al.[9] an effective vaccine against RSV has the potential to not only have a direct impact on inpatient hospitalization and use of treatment (e.g., palivizumab) for the prevention of RSV

infection in infants at high risk, but also to decrease the overall disease burden of asthma by up to 11% in young children.

It should be noted that the focus of this implication is on RSV infections in the first year of life because all but two studies in the meta-analysis studied that population.

Limitations

The main limitation of this analysis is the low quality of the studies included. It was not possible to form any hypothesis concerning etiology as no randomized trials are available because it is clearly not possible to randomly assign children to an RSV infection. Also, the diagnosis was not always provided by a physician; even if the diagnosis of asthma was made by a physician, it is not clear whether the physician was blind to the presence or absence of RSV disease in infancy. Few studies dealt appropriately with confounding, and RSV was not always excluded from the control group.

Conclusions

A considerable amount of scientific literature is dedicated to quantifying the connection between RSV disease in the first 3 years of life and subsequent asthma/wheezing. Our meta-analysis showed that the association is strong but tends to decrease with age at follow-up. The association did not depend significantly on appropriate blinding, use of confounding methodology, disease definition, or medical diagnosis. If the association is causal, an effective vaccine or a treatment against RSV infections early in life could substantially decrease the burden of asthma in the USA and would be medically important.

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TABLE 1. Characteristics of Unique Studies

Study	Country	Outcome	Diagnosis	Outcome occurrence	Inpatient age (months)*	Age at follow-up (years)*	Individuals (n)		
							Index (RSV+)	Control (RSV-)	Total
Sims et al. (1978)[48]	UK	Wheezing	Parents	Last 24 months	N/A (≤12)	8	35	35	70
Mok and Simpson (1982)[52]	UK	Asthma	Unclear	Last 12 months	4	7	100	200	300
Pullan and Hey (1982)[46]	UK	Recurrent wheezing	Unclear	Last 12 months	3	10	130	111	241
Murray et al. (1992)[53]	UK	Wheezing	Unclear	Last 12 months	4	6	42	73	115
Osundwa et al. (1993)[54]	Qatar	Recurrent wheezing	Physicians	Last 24 months	4	2	70	70	140
Korppi et al. (1994)[22]	Finland	Asthma	Physicians	Last 12 months	N/A (≤24)	9	32	52	84

Sigurs et al. (1995)[20]	Sweden	Wheezing	Physicians	Last 12 months	4	3	47	93	140
Stein et al. (1999)[23]	USA (AZ)	Recurrent wheezing	Parents	Last 12 months	N/A (≤36)	6	207	681	888
Schauer et al. (2002)[47]	Germany	Recurrent wheezing	Unclear	Last 12 months	4	1	42	84	126
Juntti et al. (2003)[45]	Finland	Asthma	Physicians	At any time	4	8	76	76	152
Singleton et al. (2003)[55]	USA (AK)	Wheezing	Physicians	Last 12 months	8	6	95	113	208
Fjaerli et al. (2005)[50]	Norway	Asthma	Physicians	Last 12 months	5	7	35	64	99
Henderson et al. (2005)[51]	UK	Asthma	Physicians	At any time	N/A (≤12)	8	73	8039	8112
Escobar et al. (2010)[49]	USA (CA)	Asthma	Physicians	Last 12 months	N/A (≤12)	3	459	70 643	71 102
Mikalsen et	Norway	Asthma	Unclear	Last 12	3	11	90	141	231

al. (2012)[76]	months

*Average for the index group.

AK indicates Alaska; AZ, Arizona; CA, California; N/A, not available; RSV+, hospitalized for respiratory syncytial virus infection in early life; RSV-, not hospitalized for respiratory syncytial virus infection in early life.

TABLE 2. Results of the Stratified Meta-Analysis (Fixed-Effects Models)

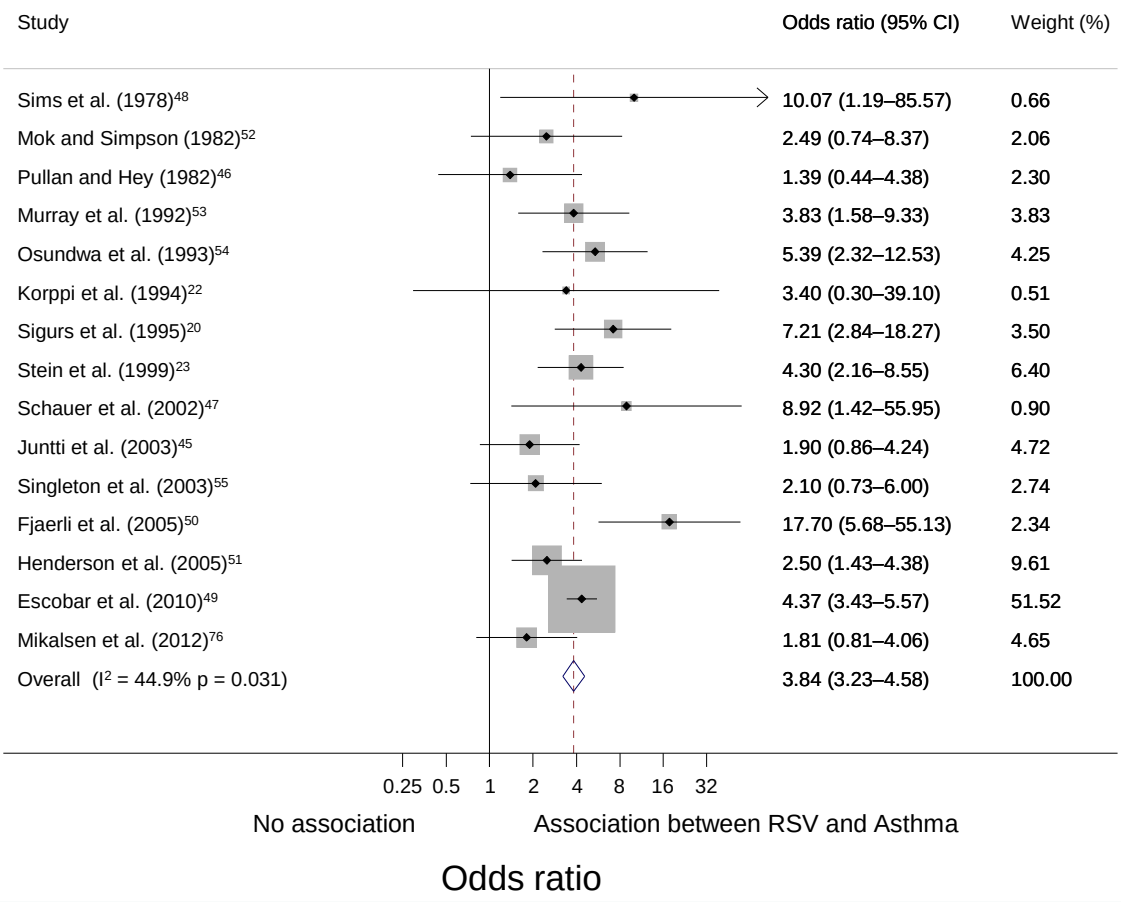
Variable	Total No. of Studies	Total No. of patients	Odds Ratio (95% CI)	I^2 (%)	Test of Heterogeneity Between Groups
All trials	15	82 008	3.84 (3.23–4.58)	45	–
Age at follow-up					0.01
≤5 years	4	71 508	4.61 (3.69–5.77)	0	
>5 years	11	10 500	2.92 (2.22–3.84)	42	
Diagnosis by					0.20
Parents/mixed/unclear	7	1971	3.08 (2.10–4.51)	17	
Physicians	8	80 037	4.08 (3.35–4.96)	58	
Disease definition					0.67
Asthma/recurrent wheezing	11	81 475	3.79 (3.16–4.56)	54	
Wheezing	4	533	4.29 (2.52–7.29)	18	
RSV in control group					0.19
Yes/maybe	3	441	2.42 (1.19–4.91)	20	

No	12	81 567	3.96 (3.31–4.74)	48	
Appropriate confounders considered					0.02
Yes	5	80 341	4.34 (3.55–5.32)	63	
No/unclear	10	1667	2.75 (1.96–3.85)	5	

CI indicates confidence interval; RSV, respiratory syncytial virus.

Figures

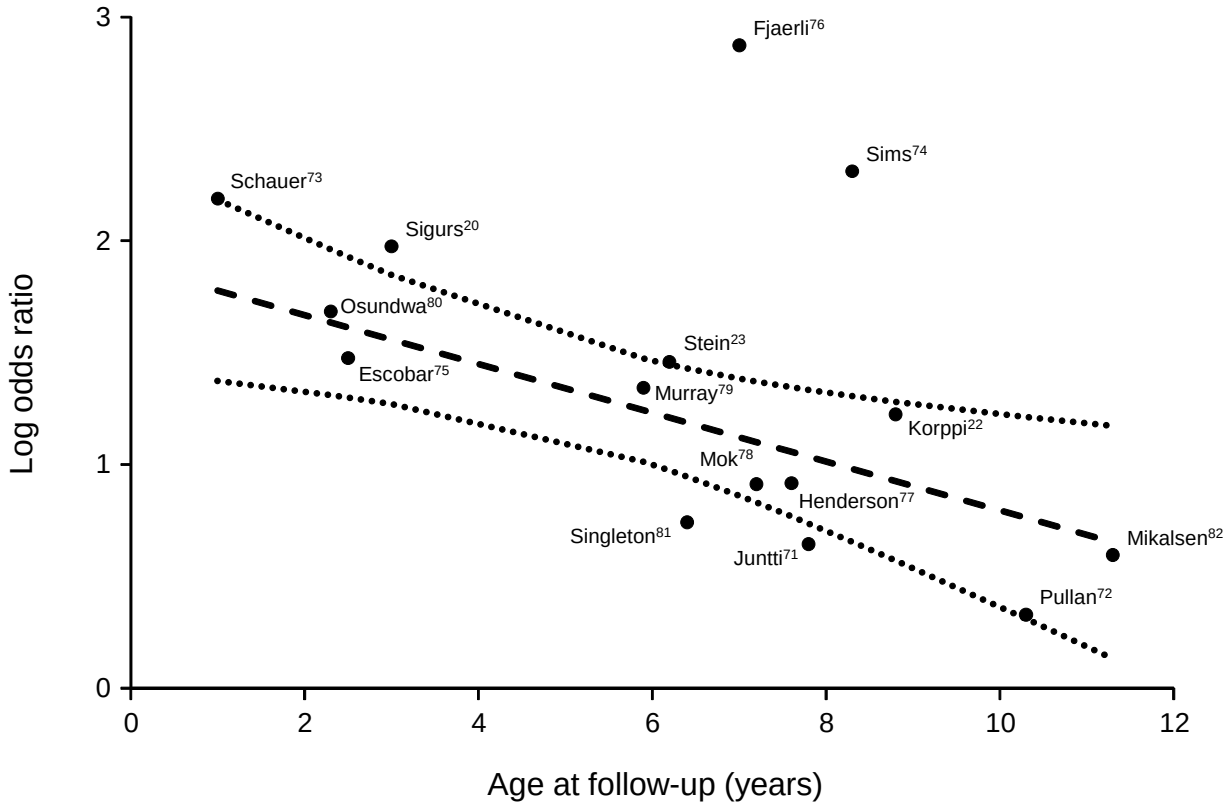
FIGURE 1. Forest plot of 15 studies assessing the impact of RSV hospitalization.



The size of the boxes is proportional to the weights used in the analysis (fixed effect); the horizontal lines represent the 95% CI.

CI indicates confidence interval; RSV, respiratory syncytial virus.

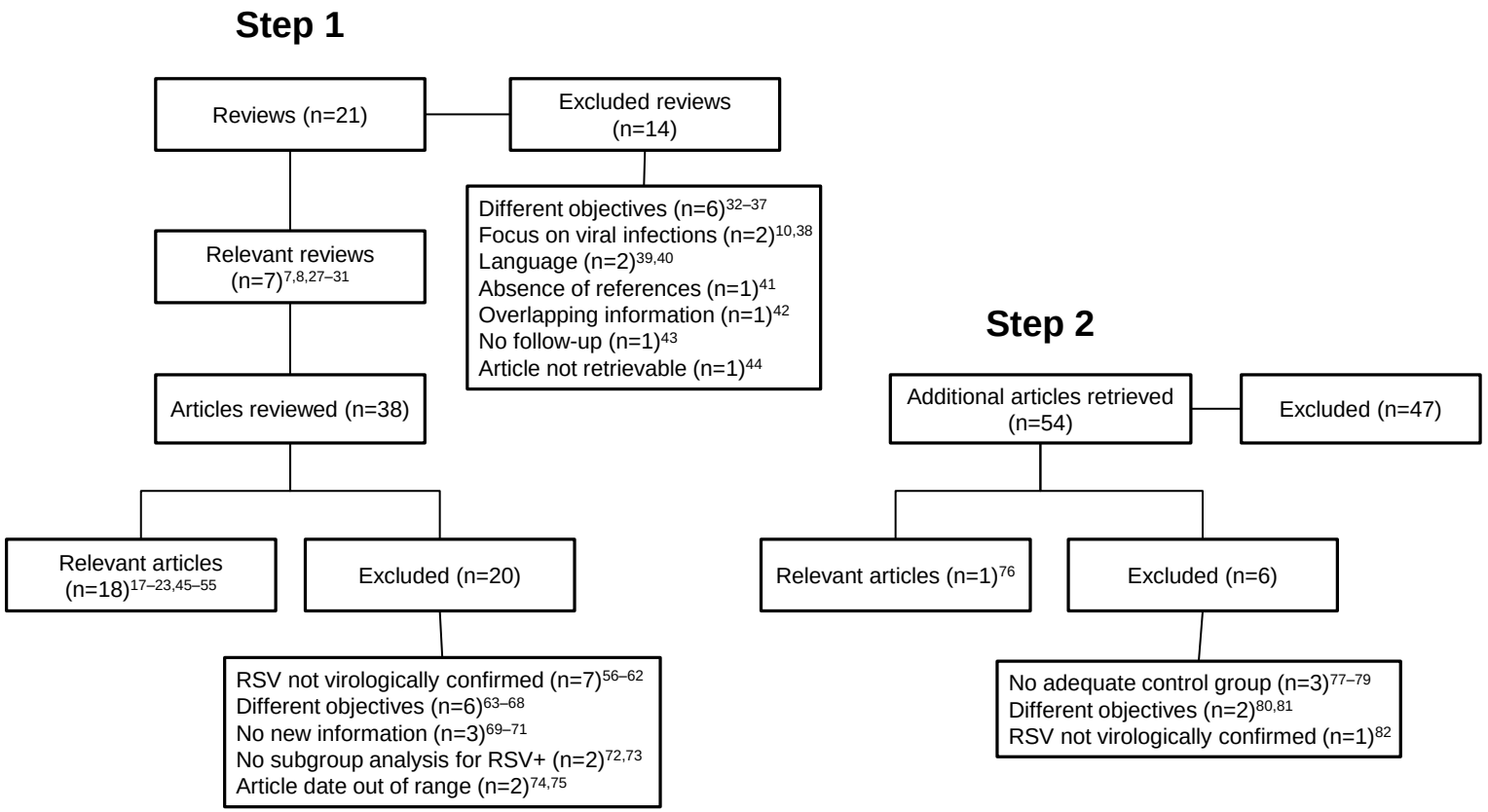
FIGURE 2. Association between respiratory syncytial virus hospitalization and asthma/wheezing: effects according to age at follow-up.



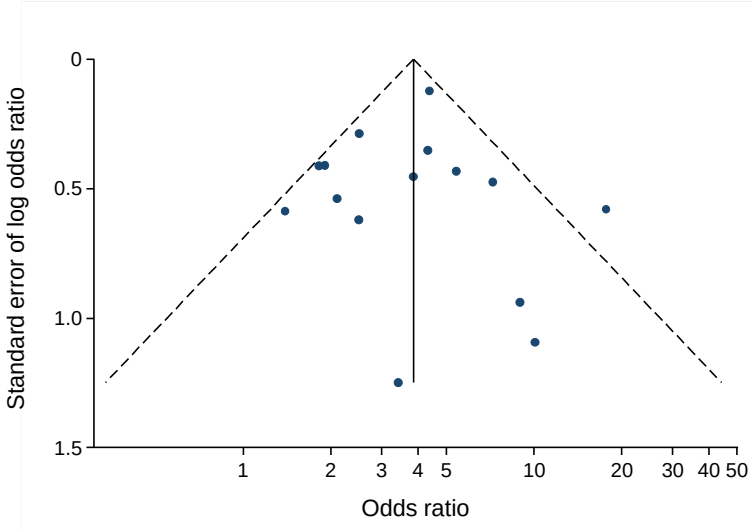
The dashed line represents the predicted effect from the meta-regression that used age at follow-up as the independent variable. Dotted lines represent the 95% confidence interval. Each circle represents an individual study.

Supplementary material

Flow chart for the process of selecting and evaluating relevant articles. RSV indicates respiratory syncytial virus.



Funnel plot of effect size versus odds ratio (log scale). The dotted lines represent pseudo 95% confidence limits.



Supplemental Digital Content

Search strategies (conducted on August 1, 2012)

Step 1

Search strategy for MEDLINE:

"Asthma/etiology" [Mesh] AND "Respiratory Syncytial Virus Infections/complications"[Mesh]

Limits: Systematic Reviews or Meta-Analysis, All Infant: birth–23 months, All Child: 0–18 years, Publication Date from 2000 to 2012.

Or ("Asthma/etiology"[Majr]) AND "Respiratory Syncytial Virus Infections/complications"[Majr]

Limits: Review, All Infant: birth–23 months, All Child: 0–18 years, Publication Date from 2000 to 2012.

Search strategy for EMBASE:

1. Respiratory Syncytial Virus.af.
2. asthma/et [Etiology]
3. 1 and 2
4. limit 3 to yr="2000–2012"
5. limit 4 to (meta analysis or "systematic review")
6. limit 4 to ("review" and (infant or preschool child <1 to 6 years>))
7. 5 or 6

Note: Reviews identified in the first step were included if they met the following criteria: (i) they identified articles that quantified the level of association between RSV infection and asthma/wheezing sequelae; (ii) the maximum age at the time of RSV infection was <3 years; (iii) articles in the review were properly referenced; (iv) the focus of the review was RSV and not other viral infections; and (v) a clinical outcome (not a laboratory test) was measured.

Step 2

Search strategy for MEDLINE:

(Respiratory Syncytial Virus or RSV) AND (Asthma OR wheezing) and (association or caus* or relationship)

Limits: Humans, All Infant: birth–23 months, All Child: 0–18 years. Field: Title/Abstract

Note: We only searched for articles that were published after the articles identified in the first step (i.e,. from November 2010 to August 2012).

Search strategy for EMBASE:

1. (respiratory syncytial virus and (asthma or wheezing) and (association or caus* or relationship)).ab.
2. limit 1 to yr="2010–Current"
3. limit 2 to (human and (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years>))

WinBUGS simulation details

Known distributions

prevalence ~dbeta(116, 1818) (i.e., mean=6.0% and SD=0.54%)

rsv.incidence ~dbeta(17 879 * 75.3%, 17 879/1.74% – 17 879 * 75.3%) [23]

ln(or) ~dnorm(1.529312, 76.408)

Where *prevalence* is the asthma prevalence for all infants <5 years old, *rsv.incidence* is the inpatient hospitalization rate in the first year of life, and *dbeta* (116, 1818) is a beta distribution with alpha = 116 and beta = 1818.

The parameters were chosen such that the mean and SD of the prevalence were 6.0% and 0.54%, respectively, as per the National Center for Health Statistics.[22]

Alpha and beta parameters for *rsv.incidence* were estimated from unprojected inpatient hospitalizations due to RSV in the first year of life and the average incidence of RSV reported by Paramore et al.[23]

or is the odds ratio of the increased association of asthma in the first 5 years and RSV hospitalization (calculated from meta-analysis).

Estimated distributions

asthma.nonrsv ~dbeta(*alpha.nonrsv, beta.nonrsv)*

asthma.rsv ~dbeta(*alpha.rsv, beta.rsv*)

Where *asthma.rsv* is the asthma prevalence for infants <5 years old who had an inpatient hospitalization in the first year of life, and *asthma.nonrsv* is the asthma prevalence for infants <5 years old who did not have an inpatient hospitalization.

Equation system to estimate parameters of the unknown distributions, alpha.nonrsv, beta.nonrsv, alpha.rsv, and beta.rsv

alpha.nonrsv = *asthma.nonrsv* * (116 + 1818) * (1 – *rsv.incidence*)

beta.nonrsv = (116 + 1818) * (1 – *rsv.incidence*) – *alpha.nonrsv*

alpha.rsv = *or* * *alpha.nonrsv* / *beta.nonrsv* * *beta.rsv*

beta.rsv = 1818 – *beta.nonrsv*

How Does Drug Coverage Vary By Insurance Type? Analysis of Drug Formularies in the USA.

Régnier SA

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Abstract

Objectives: To quantify how access to on-patent drugs by tier placement varies by insurance type and therapeutic area.

Study Design: Retrospective analysis of insurance plan drug coverage data.

Methods: Drug coverage information was collected from the Fingertip Formulary database in May 2011 for three drug classes (statins, angiotensin II receptor blockers, and protein-tyrosine kinase inhibitors) across three therapeutic areas with varying levels of generic drug availability. A generalized linear model was used to estimate the percentage of available on-patent drugs covered in the formulary tiers with lowest copay requirements (tiers 1 and 2) in different types of healthcare insurance plans in the USA.

Results: There were substantial differences between insurance types in the number of on-patent drugs reimbursed in tiers 1 and 2 (i.e. with a low copay). Compared with commercial plans, there were more on-patent drugs reimbursed with a low copay in employer plans, union plans, and with pharmacy benefit management companies, and substantially fewer on-patent drugs with a low copay in Medicare plans (Medicare Advantage, special needs, prescription drug plans) and discount prescription programs. These results were expected as union plans are known for their generosity and Medicare plans rely heavily on cost containment, eg, cost sharing. For commercial Medicaid and municipal plans, the findings were dependent on the therapeutic class or were inconclusive. The number of competitors a plan faces did not consistently affect the coverage of on-patent drugs.

Conclusions: The degree of coverage of on-patent drugs in the lowest copay tiers varies dramatically between insurance types, especially for expensive protein-tyrosine kinase inhibitors.

Word count: 256

Key words: Drug coverage, tier, generalized linear model, logit model, insurance type, competition

Abbreviations

AIC, Akaike's information criterion; *ARBs*, angiotensin II receptor blockers; *CML*, chronic myeloid leukemia; *HMG*, 3-hydroxy-3-methylglutaryl coenzyme A; *HMO*, health maintenance organization; *HIE*, health insurance experiment; *HMO*, health maintenance organization; *GLM*, generalized linear model; *MA*, Medicare Advantage; *PBM*, pharmacy benefit management; *PDP*, prescription drug plan; *PPO*, preferred-provider organization; *P-TKIs*, protein-tyrosine kinase inhibitors; *SN*, special needs.

1. Background and objectives

In the USA in 2010, approximately 63% of the population who had health insurance were insured through private schemes, 24% by government health programs and 13% by both types of programs.[1] The vast majority (approximately 85%) of privately insured Americans had access to health insurance through private employers.[1]

The main government programs are Medicaid and Medicare, covering 19% and 17% of the insured population, respectively. Medicaid is available to certain low-income individuals and families. Medicare provides health insurance for individuals older than 65 years, those younger than 65 years with certain disabilities and people with end-stage renal disease. Additional information of source of health insurance can be found in online appendix 1.

Health plans usually assign the drugs that they cover to "tiers". A drug's tier determines the degree to which the patient will have to contribute a payment for the drug – the lower the tier, the lower the copayment. Tier 1 is typically for generics, tier 2 for preferred brand-name drugs, tier 3 for non-preferred brand-name drugs and tiers 4 (and above) for coinsurance brands. Fixed-sum copayments are required from patients for drugs in tiers 1–3 to cover some of the drug costs. Coinsurance copayments are a percentage of a drug costs and vary from drugs to drugs. An individual plan may include patent-protected brand-name ("on-patent") drugs, brand-name drugs that are no longer patent protected ("off-patent") and generic bioequivalents. For individuals receiving health care coverage via employment, the average 2012 copayment was $10 for first-tier drugs, $29 for second tier drugs, $51 for third-tier drugs, and $79 for fourth-tier drugs. [2] In 2009, the average Medicare Part D copayment was $10 for first-tier drugs, $37 for second tier

drugs, $75 otherwise.[3] The Medicare Part D coinsurance rate on the specialty tier ranged from 25 percent to as high as 33 percent with a median of 30%.[3] The drugs assigned to each tier vary with individual healthcare plans and this is one of the aspects of a plan on which the consumer may base their decision when choosing a plan.

From a patient's perspective, plans that offer drugs relevant to their condition in the low copay tiers are likely to be more attractive, assuming the monthly premiums are comparable. Another factor that might make a plan more favorable is the degree of choice of drugs within a therapeutic class in the low copay tiers. The ability to choose (doctors, hospitals and drugs) is seen as very important or extremely important by the vast majority of Americans when selecting plans.[4] Evidence that the level of copayments for a given medication impacts the choice of health plans or pharmacies is however limited. Zhang and Zou (2012) found that only 5% of Medicare Part D beneficiaries chose the cheapest plan available in their region given their medication needs.[5] Lindon et al. (2007) found that 22% of Department of Defense beneficiaries over 65 years used the option with less copay.[6] The ability to choose a drug may have implications for patient adherence to prescribed medication regimens. In particular, having access to and a choice of, on-patent drugs at a reasonable copay level may be an important factor, eg, for patients who have concerns regarding drug switching or generic substitution. There is evidence that increasing a drug's copayment can decrease its utilization level, reduce adherence,[7] or lead patients to switch drugs.[8]

The objective of this study was to assess whether the level of on-patent drug coverage varies according to the following hypotheses: (1) Plan type. Some categories of plans (including some union plans) were expected to offer health insurance packages with generous benefits such as

absence of copayments, deductibles, or prior authorizations, even for on-patent drugs for which an alternative generic is available. Those plans can be costly to employers, in which case they would be called "Cadillac plans".[9,10] In such plans, a range of on-patent drugs might be assigned to lower tiers. (2) Therapeutic class. The proportion of on-patent drugs covered by the plan (as a percentage of all on-patent drugs available in the same class) would be expected to be low in therapeutic classes where there are a large number of drugs available. For those therapeutic areas, managed care organizations could be effective and aggressive in managing formularies and in influencing physicians' prescribing behavior. [11]

The implications of the analysis are important for: (1) insurees/employers who, when choosing insurance want to know whether certain types of plans provide more choice compared with others; (2) lawmakers who want to understand the impact on drug choice of curbing the use of "Cadillac plans"; (3) public health specialists who want to understand whether the population has affordable access to life-saving medications.

To date the published literature reporting on drug tiers and formularies in the USA has focused mainly on: the decrease on drug utilization after a copayment increase[12-15]; the association between the formulary position (tier) and value of a drug[16]; and the decision-making process in assigning a drug to a tier.[17-20] For instance, Linton et al. (2009) observed that the esomeprazole (Nexium) share of the proton-pump inhibitor market dropped from 20.0% to 15.7% in the month after TRICARE moved esomeprazole from tier 2 to tier 3 (copay increased from $9 to $22).[13] Similarly, in the antidepressant market, Hodgkin et al. (2008) found that drugs that became non-preferred in insurance plans experienced a decrease of 11% in the number of prescriptions filled per enrollee (vs. an increase of 5% in the comparison group).[14] No articles

have reported on the differences in coverage between insurance type and therapeutic classes. By analyzing such differences, this paper contributes to the more limited literature that advises patients on identifying plans that have limited drug formularies[21] and whether formularies meet the needs of all patients.[22,23]

2. Methods

This was a retrospective database study.

2.1 Data description

The dataset used was the Fingertip Formulary® (Fingertip Formulary LLC, Glen Rock, NJ), which is a collection of drug-coverage data for 1,768 health plans in the United States. Fingertip Formulary LLC estimates that between 95% to 98% of the covered lives in the USA are in the database. The data were collected from health plans' websites or by directly contacting the health plan providers. The information changes regularly; the data used in this paper were downloaded on May 15, 2011. While drug coverage typically changes once a year (before members enroll), it could change during the year if there is a market event (e.g. an on-patent drug loses patent) and or if the contract with a manufacturer was not renewed. The author accessed the website on May 15, 2011 and downloaded the information available that day. Since no ARBs and no P-TKIs lost patent that year, it is likely that the conclusions would not have changed dramatically in 2011. The HMGs conclusions would have remained valid for most 2011 since Lipitor lost its patent on November, 30 2011.

Fingertip Formulary data include a number of fields that are identical for all drugs: (1) health plan identifier; (2) provider (ie, company providing the health plan) identifier; (3) state(s) where the health plan operated; (4) lives covered (ie, number of enrollees in the plan) (5) plan/insurance type [commercial, PBM, employer, Medicare Advantage (MA), Medicare PDP, SN, state Medicaid, commercial Medicaid plan (if the Medicaid plan was contracted to private health companies), union, municipal, discount prescription programs]. In Fingertip Formulary, employer plans are those offered by organizations that arrange pharmaceutical benefits for its workers as part of their total benefit plan and whose data Fingertip Formulary can source in an ongoing basis. Commercial plans are set by non-Medicare and non-Medicaid organizations that offer pharmaceutical benefits to individuals and/or groups such as businesses, local governments, etc. The database allows for information to be included on the tier status (whether a drug is in tiers 1–6, not reimbursed, or not available) for each drug within each plan. Online appendix 2 provides the number of plans and the number of insured individuals for each insurance type.

Three different therapeutic classes with different levels of generic competition and disease burden were analyzed in this paper: (1) Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; HMGs), used to lower serum cholesterol levels; (2) angiotensin II receptor blockers (ARBs), used to reduce hypertension; and (3) protein-tyrosine kinase inhibitors (P-TKIs), which are treatments for chronic myeloid leukemia (CML) and gastrointestinal stromal tumor. At the time of the data download, the HMG class comprised four off-patent products that had generic equivalents and eight on-patent products. Six ARBs had patent protection and one ARB was available off-patent and as a generic equivalent. [Edarbi® (azilsartan medoxomil) had only recently been launched and was not included in the analysis as no information was available

for it in a number of plans.] All available P-TKIs were still within patent and no generic versions were available. Coinsurance copays were much higher for P-TKIs than HMGs and ARBs. For instance, if the coinsurance rate was 30%, the average 2011 copay for a 30-day supply was $1,820 for imatinib mesylate (Gleevec®), $56 for atorvastatin 80mg (Lipitor®) and $48 for Valsartan Hydrochlorothiazide 320 mg-25 mg (Diovan HCT®).[24]

2.2 The model

The model's objective was to explain how the number of on-patent drugs in a low tier varies by insurance type (eg, commercial, municipal, Medicare, etc.) and therapeutic area. The level of drug coverage could be defined in several ways: number of reimbursed drugs, number of reimbursed on-patent drugs, number of drugs with a low-tier copay, number of on-patent drugs with a low-tier copay, etc. Because generics are typically reimbursed and/or are affordable, the focus was on on-patent products. Therefore, coverage was defined as the number of drugs with patent protection that were in a low copay tier (ie tiers 1 or 2) and is referred to as "on-patent drug coverage" hereafter. Medicare PDP, MA and SN plans were grouped into a Medicare variable.

A logit regression was used to explain drug coverage. Tobit and count models were also considered to ensure that the findings did not depend on the methodology. More details on the models can be found in online appendix 3. Plans without coverage information for all products in a therapeutic area were excluded for such analyses. On-patent drugs used in the analysis are shown in online appendix 4.

Generalized linear model

A generalized linear model (GLM) with a logit link function was used to examine the relationship between the percentage of available on-patent drugs in a therapeutic area that are covered in tiers 1 or 2 and the variables of interest: insurance type and therapeutic areas. Hosmer–Lemeshow and Pregibon link tests were used to ensure that the model adequately fit the data.

Count model

Use of Poisson or negative binomial regressions was also considered as the number of on-patent drugs with favorable tier coverage was a count variable. However, the Poisson distribution was not deemed relevant because the distributions were over dispersed (online appendix 5). Therefore, only a negative binomial model was analyzed.

Censored model

Drug-coverage data can be considered right-censored as the number of covered drugs was, by definition, bound by the number of approved brands. Therefore, applying a censored model (Tobit regression) would be appropriate. Intuitively, a censored model should be more relevant for therapeutic classes with few or no interchangeable options. In this case, one could assume that insurance companies would be willing to cover more drugs if more were available. The high number of plans covering all four P-TKIs was consistent with this hypothesis. As the number of approved drugs was specific to each therapeutic area, a Tobit model was run separately for HMGs, ARBs and P-TKIs. As the assumption of normality of the residuals was rejected (ie, the maximum-likelihood estimator was inconsistent), a bootstrap approach was used (with 1,000 replications at 95% confidence level).

Statistical analysis

All analyses were performed using the statistical analysis program Stata, version 12.1 (StataCorp LP, College Station, TX, USA).

3. Results

Table 2 shows the average, across all plans, of the number of drugs in each tier. The numbers were calculated by first extracting, from the database, the number of drugs by tier for each plan. Then, for each tier, the average, across all 1,768 plans, of the number of drugs was calculated. The results can be interpreted in terms of how the drugs are split across tiers. On average, 4.7 HMGs and 2.1 ARBs were not reimbursed. Most P-TKIs were reimbursed by health plans; an average of only 0.5 drug (out of 4 available drugs, i.e. 12%) was not reimbursed by health plans. HMGs and ARBs were rarely assigned to tiers 4 and above (average 3% of available ARBs and HMGs were in such tiers) but P-TKIs were more frequently found in these tiers (average 31% of available P-TKIs). As expected, on-patent drugs were rarely in tier 1 because it is typically reserved for generics. On average, approximately 30% of on-patent ARBs and HMGs were not reimbursed by health insurance plans. The proportion of on-patent drugs in tier 2 was similar across therapeutic classes (34–39%) but tier 3 was used much less for on-patent P-TKIs than for on-patent HMGs or ARBs (9% vs 26% and 30%, respectively).

On-patent drug coverage varied greatly by plan type (Table 3). Across therapeutic areas, discount prescription programs and Medicare plans offered the lowest number of on-patent drugs in tiers 1 and 2, especially for P-TKIs. P-TKIs were often in tier 4 or higher in Medicare plans, meaning that a coinsurance was required, likely due to their relatively high cost [eg, in 2011 the

average wholesale price of the P-TKI imatinib mesylate (Gleevec®) was $202 per day for patients with chronic-phase Philadelphia chromosome-positive CML[24,25]]. Union and municipal plans had on-patent many HMGs in tier 1 or 2 (ie, the lowest copay tiers), which seems to corroborate the assumption that those plans offer generous drug benefits. Commercial Medicaid plans placed a high proportion of the on-patent drugs in the lowest copay tiers. The results for state Medicaid will be further discussed in the Summary and Discussion section.

Table 4 shows summary statistics for the independent variables used in the model specifications. Commercial plans were the most prevalent plans in the database. PBMs were the plans with the most enrollees, on average. The variable capturing the number of competitors is also called "plan competition" in the remainder of the article. Its calculation can be found in online appendix 6. The categories of plans with the highest number of competitors were PBMs and Medicare PDP.

3.1 Generalized linear model

The results of the GLM regression are presented in Table 4. The reference categories for plan and therapeutic dummies were commercial plans and HMGs, respectively. A positive coefficient sign indicates an increased probability of on-patent drug coverage in a low tier. On average, 40.1% of on-patent drugs were in a low tier. All variables were highly significant and therefore had an impact on the probability that an on-patent drug had a low copay requirement. The average marginal effect of P-TKIs represents the incremental probability, relative to HMGs, of on-patent PTKIs to be covered in a low tier. The value was +5.6 points and the branded P-TKIs were predicted to be in a low tier in 44.8% of cases vs 39.0% for HMGs. The marginal effect

was -2.4 points for on-patent ARBs which were predicted to be in a low tier in 36.7% of cases. On average, the percentage of on-patent drugs in tiers 1 or 2 was 20 points higher for union plans and 74 points higher for state Medicaid than for commercial plans. All else being equal, PBMs, commercial Medicaid, employer and municipal plans also covered more on-patent drugs with a low copay than did commercial plans. However, Medicare on-patent drug coverage in tiers 1 or 2 was substantially lower than that of commercial plans (-23 points). If we do not control for the differences between plans, the conclusion remains that PTKIs (respectively ARBs) have higher (respectively lower) probability of on-patent drug coverage in a low tier than HMGs ($p<0.001$).

3.2 Model specification

Additional covariates

Medicare plans had relatively few on-patent drugs in tiers 1 and 2 for P-TKIs (Table 2). Conversely, commercial Medicaid and employer plans had a high number of P-TKIs with a low copay. Interaction variables were therefore introduced between P-TKIs and Medicare, commercial Medicaid, and employer plans. The number of competitors a plan faces was introduced since high levels of competition could impact drug coverage in two opposite ways: by triggering a drug "arms race" to attract enrollees or by leading to cost and drug control. Interaction variables between plans' competition and therapeutic areas were introduced to investigate whether the competition impact varied by therapeutic area.

Table 4 shows the impact of introducing additional variables (see online appendix 3 for additional details). As expected, the sums of the coefficients for P-TKI and for the interaction between the Medicare/commercial Medicaid plans and PTKI were negative and positive

respectively ($p<0.001$), which means that Medicare (respectively commercial Medicaid) plans covered fewer (respectively more) PTKIs than HMGs in a low tier. In other words, Medicare plans had a substantially lower proportion of P-TKIs than on-patent HMGs in tier 1 or 2. Commercial Medicaid plans were less restrictive for P-TKIs than for HMGs. The average number of competitor plans had a significant negative effect for P-TKIs ($p=0.05$). The more competition faced by plans, the less likely they were to cover P-TKIs in the low copay tiers. However, the number of competitor plans did not impact coverage of on-patent ARBs differently than that of HMGs. Overall, the number of competitors was not significant across therapeutic areas (F-test $P=0.15$). The other variables remained significant, with similar coefficient values. The interaction variables added some information to the core model (Akaike's information criterion [AIC] of 0.99 vs 0.96, respectively).

Finally, a variable measuring the number of insured lives by plan was introduced to assess whether the size of a plan had an impact on on-patent drug coverage. The hypothesis was that larger plans had lower general marketing expenses (as percentage of sales) due to economies of scale and could afford to cover more on-patent drugs in tiers 1 and 2. The variable measuring insured lives was significant and positive, meaning that plans with more enrollees covered, on average, more on-patent drugs in tiers 1 and 2. All variables remained significant after adding this variable and analyzing a subset of the original dataset. One variable (commercial Medicaid) experienced a significant switch in sign. The regression did not include municipal plans or discount prescription programs since only one of 14 discount prescription programs and 79 of 235 municipal plans had information on lives covered. Since the dataset with lives data is only a

subset of the universe, care must be taken when comparing the results, in particular AIC, of previous regressions.

Logit model specification tests

The logistic model with interaction terms passed the Pregibon link test but not the Hosmer–Lemeshow test (F-test P=.46 and P=.01, respectively). The model with interaction terms and lives covered variable passed both tests (F-test P=.85 and P=.23, respectively) and its goodness of fit was not rejected.

Finally, a bootstrap estimation (using 1,000 bootstrap replications at 95% confidence level) was performed for the GLM with interaction variables. The coefficients from the bootstrap estimates were found to be similar to those of the GLM. The only difference was that the commercial Medicaid variable became significant. Based on these results, the coefficients' estimates and significance levels from the GLMs were not driven by outliers.

Tobit and negative binomial models

The sign and significance of coefficients were similar for the Tobit and negative binomial models (Table 5). The sign and significance of coefficients were also similar to those of the logit model (Table 6).

4. Summary and Discussion

To the author's knowledge, this article is the first report of an attempt to analyze drug-tier data in this way. Across all models and therapeutic areas, Medicare plans and discount prescription programs had consistently fewer on-patent drugs in the lowest copay tiers than did commercial plans. These results were expected. The revenue per enrollee of Medicare PDP and

MA plans is capped since these plan providers have to offer standard plan designs (or designs at least actuarially equivalent to the standard plan designs). Therefore, those plans may try to contain costs to increase profits. Discount prescription programs are basic drug-insurance programs that mainly cover generics. Conversely, PBMs, employer, and union plans had higher on-patent drug coverage than commercial plans. Therefore, employees had access to more on-patent drugs in the low copay tiers when companies outsourced pharmacy benefits to a PBM and when companies created their own formulary. State Medicaid covered more on-patent drugs in a low-copay tier than any other types of plans. This result reflects the fact that 46 out of 49 Medicaid plans only had 2 tiers. In addition, only one Medicaid plan (Mi Salud, Puerto Rico Medicaid) did not reimburse all on-patent drugs. One explanation could be that 2 tiers may be enough to convince patients to use drugs in tier 1 since a marginal copay difference may dissuade patients on low incomes from using a drug. Alternatively, Medicaid plans may have high bargaining power and/or pharmaceutical companies may be willing to offer substantial rebates to grant access to this segment of the population. Medicaid administrators may also limit cost-sharing for on-patent drugs so that cost is not a barrier to compliance with treatment regimens.

The significance of coefficients for commercial Medicaid and municipal plans varied by therapeutic area and/or methods. Commercial Medicaid plans covered, on average, more P-TKIs (all within patent) than did commercial plans. This was not the case for HMGs (Table 5). One explanation may be that state Medicaid agencies, when negotiating with commercial Medicaid companies, may include clauses regarding maximum allowable costs sharing for classes with generics.

Across all plans, the percentage of on-patent drugs covered in a low tier was substantially higher for P-TKIs than for HMGs and ARBs, despite P-TKIs being more expensive. One explanation might be that the high unmet medical need associated with CML justifies an affordable choice (ie, the clinical data outweigh the economics). On-patent ARBs were slightly less well covered than on-patent HMGs, despite a lower degree of generic competition. Plan providers might consider that other classes of antihypertensives, eg, calcium channel blockers or beta-blockers, are acceptable alternatives to ARBs and thus do not feel compelled to place numerous drugs in tiers 1 or 2.

Plan competition had a negative impact on P-TKI coverage but no significant impact on on-patent ARB or HMG coverage. In other words, when on-patent drugs were more scarce and expensive (such as P-TKIs), plans in competitive states limited the number of on-patent drugs with a low copay, possibly to reduce costs.

The key findings were robust: the coefficients' signs and significance levels remained similar for the core variables when: (1) additional covariates were added; (2) alternative models were applied; and (3) subsets of data were analyzed. Additionally, the most comprehensive logit model passed the goodness-of-fit tests.

The analysis presented in this paper could have some public health implications. Newhouse argued that the optimal cost-sharing indicated by the RAND health insurance experiment (HIE) (25% coinsurance) may be suboptimal for medications for chronic diseases, especially medications whose benefits only become apparent in the long term.[26,27] For instance, Goldman et al. found that compliance with cholesterol-lowering therapy was associated with a reduction in the annual rate of hospitalization. However, they also found that higher levels of cost-sharing

were associated with a reduction in compliance.[28] As such, Medicare plan designs may be suboptimal because they rely heavily on cost-sharing (ie, tier 4) for expensive, chronic therapies such as P-TKIs.

5. Limitations

There were some limitations in the data: (1) Coverage information was not complete for all plans. For example, of 1,768 plans in the database, 1,579 plans had coverage information for all on-patent HMGs, 1,673 for all ARBs and 1,631 for all P-TKIs. Only plans that had coverage information for all on-patent drugs within a therapeutic area were included in the analysis, which could, therefore, suffer from censoring issues. 39% of the plans that did not have information for all HMGs were commercial plans and 29% were employer plans. In the whole Fingertip database, commercial and employer plans represent 22% and 11% of the plans, respectively. There was a high overlap, across therapeutic areas, between plans without coverage information for all products. For instance, 92% of the plans that did not have coverage information for all ARBs did not have information for all HMGs. (2) Clear conclusions for municipal plans could not be derived because they are heterogeneous, as described in the Background and Objectives sections. (3) Only 11 union plans were included, which made it difficult to draw robust conclusions. If prescription data were available, a Herfindahl index based on the market share of plans may be a better measure of competition than a plan count.

Finally, the analysis was a snapshot of the situation in 2011. As more generics launch in each therapeutic area and more new drugs become available, the results of this study may not be applicable.

6. Conclusions

Compared with commercial plans, the level of on-patent drug coverage was consistently higher in employer, union, and PBM plans, and consistently lower in Medicare plans. One implication would be to reconsider coverage by Medicare plans for chronic therapeutic diseases with high costs. Patients enrolled with Medicaid (ie, the economically poorest segment of the population) had excellent on-patent drug coverage and good access to new technologies. Increased competition between plans does not reduce on-patent drug coverage for all therapeutic areas.

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Table 2. Average Number of Drugs Covered by Healthcare Insurance Plans, According to Formulary Position

	Percentage of available drugs *(Average number of drugs)* covered by plans					
	All drugs (on-patent and off-patent brand-name drugs and generics)			On-patent drugs only		
	HMGs	ARBs	P-TKIs	HMGs	ARBs	P-TKIs
Total available	**100** ***(16)***	**100** ***(8)***	**100** ***(4)***	**100** ***(8)***	**100** ***(6)***	**100** ***(4)***
Tier 1[a]	20 *(3.1)*	13 *(1.0)*	3 *(0.1)*	3 *(0.3)*	3 *(0.2)*	3 *(0.1)*
Tier 2	23 *(3.7)*	23 *(2.3)*	39 *(1.6)*	35 *(2.8*[b]*)*	34 *(2.0)*	39 *(1.6)*
Tier 3	23 *(3.6)*	27 *(2.1)*	9 *(0.4)*	26 *(2.0)*	30 *(1.8)*	9 *(0.4)*
Tier 4 and above	3 *(0.5)*	3 *(0.3)*	31 *(1.2)*	4 *(0.3)*	4 *(0.2)*	31 *(1.2)*
Not reimbursed	29 *(4.7)*	27 *(2.1)*	12 *(0.5)*	29 *(2.3)*	27 *(1.6)*	12 *(0.5)*
No information	3 *(0.5)*	2 *(0.1)*	6 *(0.3)*	3 *(0.2)*	2 *(0.1)*	6 *(0.3)*

[a]Tier 1 is the insurance plan drug-formulary tier with the lowest copay requirement and generally includes generic drugs. Tiers 2 and 3 have higher copay requirements and typically comprise preferred and non-preferred brand-name drugs, respectively. Tiers 4 and above include coinsurance tiers in which plans ask for coinsurance instead of copayments.

[b]Example calculation: On average across all the plans, there are 2.8 on-patent HMGs in tier 2. This was calculated by (1) identifying for each plan, the number of on-patent HMGs that were in tier 2 (1,768 data points); (2) calculating the average of those 1,768 data points. The percentage indicates the percentage of the total available on-patent HMGs (ie, 2.8 divided by 8).

ARB indicates angiotensin II receptor blocker; HMG, angiotensin II receptor blocker; P-TKI, protein-tyrosine kinase inhibitor.

Table 3. Percentage of On-Patent Drugs in Tier 1 or Tier 2 by Plan Type and Drug Class

Plan type	HMGs	ARBs	P-TKIs
Commercial	38%	33%	47%
Commercial Medicaid	41%	42%	70%
Discount prescription programs	0%	2%	0%
Employer	48%	41%	68%
MA	23%	22%	4%
Medicare PDP	29%	26%	8%
Medicare SN	26%	25%	24%
Municipal	51%	57%	52%
PBM	46%	45%	59%
State Medicaid	95%	95%	98%
Union	60%	52%	55%
Average across all plans	**39%**	**37%**	**42%**

Note: The average across all plans is lower than in Table 1 because not all on-patent drugs are in tier 1 or tier 2.

ARB indicates angiotensin II receptor blocker; HMG, angiotensin II receptor blocker; MA, Medicare Advantage; PBM, pharmacy benefit management; PDP, prescription drug plan; P-TKI, protein-tyrosine kinase inhibitor; SN, special needs.

Table 4. Descriptive Statistics of Independent Variables

Plan type	Number of plans	Average number of competitors		Lives covered (thousands)	
		Mean	SD	Mean	SD
Commercial	996	26.4	13.9	313	876
Commercial Medicaid	614	14.3	9.3	95	126
Discount prescription programs	39	6.5	0.9	1700	0
Employer	476	0	0	72	170
MA	913	30.8	14.2	27	118
Medicare PDP	368	46.2	6.6	149	480
Medicare SN	441	13.1	7.4	8	17
Municipal	684	13.0	5.2	258	1,018
PBM	180	52.1	1.1	3,039	5,086
State Medicaid	146	-	-	683	842
Union	26	4.0	2.0	201	150
Across sample		21.4	16.9	218	997
Observations	**4,883**	**4,883**		**3,932**	
Missing	**421**	**421**		**1,372**	

Note: The numbers differ from Table 1 since each plan could have potentially 3 observations (one per therapeutic area). In addition, out of the potential 5,304 observations (1768 × 3), only 4,883 were included; 95 records were excluded because they did not have coverage information for all ARBs, 137

were excluded for lack of information on P-TKIs and 189 were excluded for lack of information on HMGs.

ARB indicates angiotensin II receptor blocker; HMG, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; MA, Medicare Advantage; PBM, pharmacy benefit management; PDP, prescription drug plan; P-TKI, protein-tyrosine kinase inhibitor; SN, special needs.

Table 5: Logit Regression Results for the Proportion of On-Patent Brands in a Low Tier

Plan type	Regression coefficient	Average marginal effect (dc/dx), market share point	Base model + interaction + competition	Base model + interaction + competition + lives
Constant[a]	-0.39***	n.a.	-0.41***	-0.49***
Commercial Medicaid	0.41***	+8.3	0.12	-0.31*
Discount prescription programs	-15.89***	*Out-of-range*	-15.97***	[b]
Employer	0.69***	+14.1	0.28**	0.29**
State Medicaid	3.62***	+73.9	3.55***	3.54***
Medicare	-1.12***	-22.8	-0.69***	-0.55***
Municipal	0.48***	+9.9	0.44***	[b]
PBM	0.43***	+8.9	0.52***	0.71***
Union	0.99**	+20.2	0.92**	0.90*
ARB	-0.12***	-2.4	-0.06	-.16***
P-TKI	0.28***	+5.6	0.57***	1.18***
Number of competitors			-0.00	-0.00
ARB×number of competitors			-0.00	0.00
P-TKI×number of competitors			-0.01*	-0.02***

P-TKI×commercial		0.79***	0.55**
Medicaid			
P-TKI×employer		1.49***	0.99***
P-TKI×Medicare		-1.44***	-1.71***
Lives (millions)			0.04**
Observations	*4,883*	*4,883*	*3,700*
AIC	*0.99*	*0.96*	*0.89*
Predicted mean	*40.1%*		
Predicted mean (HMG)	*39.0%*		
Predicted mean (ARB)	*36.7%*		
Predicted mean (P-TKI)	*44.8%*		

Standard errors were calculated assuming that the data were clustered at the plan level; dc/dx for factor levels is the discrete change from the reference point level (HMG and commercial) to the variable of interest.

[a]The constant is the predicted log odds ratio of the percentage of on-patent HMGs in a low tier in commercial plans without competition.

[b]Discount prescriptions programs were not included since only one of 14 discount prescription programs and 79 of 235 municipal plans had information on lives covered.

*P<.05; **P<.01; ***P<.001.

AIC indicates Akaike's information criterion; ARB, angiotensin II receptor blocker; HMG, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; n.a., not applicable; PBM, pharmacy benefit management, P-TKI, protein-tyrosine kinase inhibitor.

Table 6. Tobit and Negative Binomial Results for Low-Tier On-Patent Drugs (With Robust Standard Errors)

	Tobit (bootsrap)			**Negative binomial**		
Plan type	HMGs	ARBs	P-TKIs	HMGs	ARBs	P-TKIs
Constant	3.20***	2.07***	2.67***	1.15***	0.70***	0.74***
Commercial Medicaid	0.31	0.60**	1.39***	0.06	0.21**	0.32***
Discount prescription programs	-3.20***	-2.07***	-2.67***	-22.66	-20.2	-21.29
Employer	0.98***	0.39**	2.85***	0.27***	0.18**	0.49***
State Medicaid	7.19***	5.94***	5.19	0.89***	1.04***	0.63***
Medicare	-1.23***	-0.67***	-2.20***	-0.47***	-0.37***	-1.66***
Municipal	**0.96*** **	**1.73*** **	**0.21**	**0.27*** **	**0.52*** **	**0.01**
PBM	**0.49***	**0.61*** **	**1.20***	**0.16**	**0.27***	**0.25***
Union	2.61**	1.40*	1.51	0.56*	0.49*	0.36
Observations	*1,579*	*1,673*	*1,631*	*1,579*	*1,673*	*1,631*

*P<.05; **P<.01; ***P<.001.

ARB indicates angiotensin II receptor blocker; HMG, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; PBM, pharmacy benefit management; P-TKI, protein-tyrosine kinase inhibitor.

Appendix 1: Background on health insurance in the US

Employers have numerous options for offering drug reimbursement to their employees, including using health maintenance organizations (HMOs; "commercial" insurance) to manage pharmacy benefits or outsourcing of drug coverage management to pharmacy benefit management companies (PBMs). PBMs typically manage pharmacy networks, drug-utilization reviews, outcome and disease-management programs.[29] PBMs also differ from HMOs in that they do not manage the medical benefits of the insurees. HMOs can also contract to PBMs the reimbursement and administration of dispensed drugs. Unions, such as the United Federation of Teachers, can also propose drug coverage to their members. Seniors can obtain prescription drug coverage via Medicare prescription drug plans (PDPs), which are privately administered but subsidized by the government. Alternatively, they can use Medicare Advantage (MA) plans, which function like HMOs, or preferred-provider organizations (PPOs) with prescription drug coverage.[30] Special needs (SN) plans are MA plans for individuals with certain chronic conditions or specialized needs, including those living in certain institutions such as nursing homes.[31] Other insurance plans include municipal plans, which include health plans for federal or state employees, TRICARE for military members and state-run plans that complement Medicaid and Medicare.

Appendix 2: Descriptive statistics by health insurance type

Appendix Table 1: Descriptive statistics by health insurance type

Plan type	Number (%) of plans	Lives covered, millions (%)
Commercial	382 (22)	118 (37)
Commercial (Medicaid)	212 (12)	16 (5)
Discount prescription programs	14 (1)	2 (1)
Employer	202 (11)	12 (4)
MA	315 (18)	8 (3)
Medicare PDP	128 (7)	17 (5)
Medicare SN	152 (9)	1 (<1%)
Municipal	235 (13)	21 (7)
PBM	68 (4)	85 (27)
State Medicaid	49 (3)	33 (11)
Union	11 (1)	2 (1)
Total	**1,768 (100)**	**315 (100)**

Source: Fingertip Formulary

MA, Medicare Advantage; PBM, pharmacy benefit management; PDP, prescription drug plan; SN, special needs.

Appendix 3: Model details

The objective of the modeling was to explain the following function: c=f($type_i$, j) where c was the drug coverage, $type_i$ was plan i's insurance type (eg, commercial, State Medicaid, etc), $comp_i$ was the and j was the therapeutic area.

Generalized linear model with logit link*:* A generalized linear model with a logit link function was used to examine the relationship between the percentage of on-patent drugs in a therapeutic area covered in tier 1 or tier 2 and the type of insurance, controlling for therapeutic area. Formally, the following equation was analyzed:

$$\mathrm{E}[\mathrm{Log}(\frac{MS_{i,j}}{1-MS_{i,j}})]= x_i^{'}\beta+t_j^{'}\alpha$$

Where $MS_{i,j}$ was the percentage of on-patent drugs covered (in tiers 1 or 2) by plan i for the therapeutic area j, the vector x_i contains the plan characteristics (insurance type) and the vector t_j contains the therapeutic area identifier. The coefficient vector β of this equation can be interpreted as follows: if the k^{th} component of x_i increases by one unit, the log odds ratio increases by β_k**,** on average. Therefore, positive values in β increase the odds of brands being covered. Since the same plan could potentially appear three times (once for each therapeutic area) in the dataset, standard errors were calculated assuming that the data were clustered at the plan level. Hosmer–Lemeshow and Pregibon link tests were used to ensure that logit regression models adequately fit the data. Unlike Tobit and counts models, the logit regression allowed a direct comparison of therapeutic areas because the percentage of covered drugs in tier 1 or tier 2 was analyzed. The *margins* command was used to calculate the sample predicted mean and

marginal effects. The *cluster* command was used to calculate standard errors for clustered data at the plan level.

Censored model (Tobit): Drug coverage data can be considered right-censored because the number of covered drugs was, by definition, bound by the number of approved drugs. Therefore, a censored model (Tobit regression) made intuitive sense. If c_i was the number of on-patent drugs with low-tier copays in plan *i*, c_i* the plan propensity of plan *i* to cover on-patent drugs in low tiers, and b_a the number of drugs approved on the market, the censored Tobit model could be written as:

$$c_j = \begin{cases} c_j^* \text{ if } c_j^* < b_a \\ c_u \text{ if } c_j^* \geq b_a \end{cases}$$

The *robust* command was used to calculate robust standard errors.

Negative binomial: The marginal density is $h(y|\mu,\alpha)= \int f(y|\mu,v)g(v|\alpha)dv$ where *y* is the number of drugs in tier 1 or 2, *f* is the Poisson density and *g* a gamma density with E[*v*]=1 and V[*v*]= α.

With a negative binomial distribution, $E[y_{i,j}|\mu_{i,j},\alpha]= \mu_i,=\exp(x_i'\beta+t_j'\alpha)$ and $V[y_{i,j}|\mu_{i,j},\alpha]= \mu_{ij}(1+\alpha\mu_{i,j})$ where $y_{i,j}$ is the number of on-patent drugs covered in tiers 1 or 2) by plan *i* for the therapeutic area *j*, the vector x_i contains the plan characteristics (insurance type) and the vector t_j contains the therapeutic area identifier.

Interpretation of interaction variables: The manuscript reports the signs of $E[MS_{i,j}|t_1=1,t_2=0,x_1=1]-E[MS_{i,j}|t_1=0,t_2=1,x_1=1]$, $E[MS_{i,j}|t_1=1,t_2=0,x_2=1]-E[MS_{i,j}|t_1=0,t_2=1,x_2=1]$, and $\delta E[MS_{i,j}|t_1=1]/\delta x_3$ where $MS_{i,j}$ is the percentage of on-patent drugs covered for plan *i* and

therapeutic area *j*, t_1=PTKI, t_2=HMG, x_1=Medicare, x_2=commercial Medicaid and x_3=number of competitors. Since $E(MS_{i,j})=\exp(x_i'\beta+t_j'\alpha+t_j \cdot x_i'\gamma) / [1+\exp(x_i'\beta+t_j'\alpha+t_j \cdot x_i'\gamma)]$, then $\delta E[MS_{i,j}|t_1=1]/\delta x_3$ is of the sign $\delta E[\exp(x_i'\beta+t_j'\alpha+t_j \cdot x_i'\gamma)|t_1=1]/\delta x_3=\beta_3+\gamma_{31}$ where β_3 is the GLM's coefficients of x_3 and γ_{31} is the GLM's coefficient of the interaction variable x_3*t_1. Similarly, since logit(x) is an increasing function in x, $E[MS_{i,j}|t_1=1,t_2=0,x_1=1]- E[MS_{i,j}|t_1=0,t_2=1, x_1=1]$ is of the sign of $[(x_i'\beta+t_j'\alpha+t_j \cdot x_i'\gamma)|t_1=1,t_2=0,x_1=1]- [(x_i'\beta+t_j'\alpha+t_j \cdot x_i'\gamma)|t_1=0,t_2=1,x_1=1]= \alpha_1+ \gamma_{11}$ where α_1 is the GLM's coefficients of t_1 and γ_{21} is the GLM's coefficient of the interaction variable x_1*t_1.

Appendix 4: On-patent drugs used in the analysis

Appendix Table 2: On-patent drugs used in the analysis

Therapeutic area	Brand name	Molecule
HMGs	Advicor	Niacin extended-release/lovastatin
	Caduet	Amlodipine besylate/atorvastatin
	Crestor	Rosuvastatin
	Lescol XL	Fluvastatin
	Lipitor	Atorvastatin
	Livalo	Pitavastatin
	Simcor	Niacin extended-

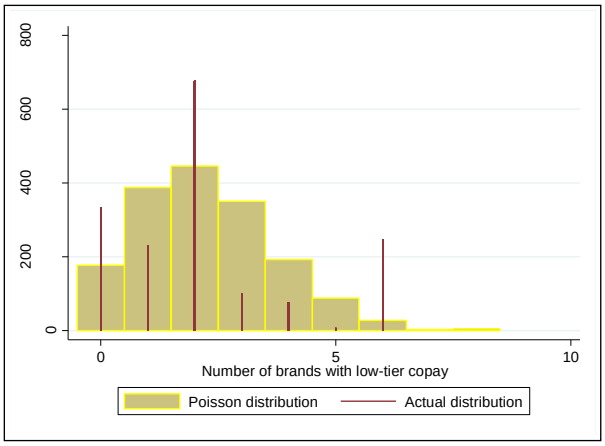
	Vytorin	release/simvastatin Ezetimibe/simvastatin
ARBs	Atacand	Candesartan cilexetil
	Avapro	Irbesartan
	Benicar	Olmesartan medoxomil
	Diovan	Valsartan
	Micardis	Telmisartan
	Teveten	Eprosartan mesylate
PTKIs	Gleevec	Imatinib
	Sprycel	Dasatinib
	Sutent	Sunitinib
	Tasigna	Nilotinib

Appendix 5: Histograms of on-patent drugs covered in low copay tiers

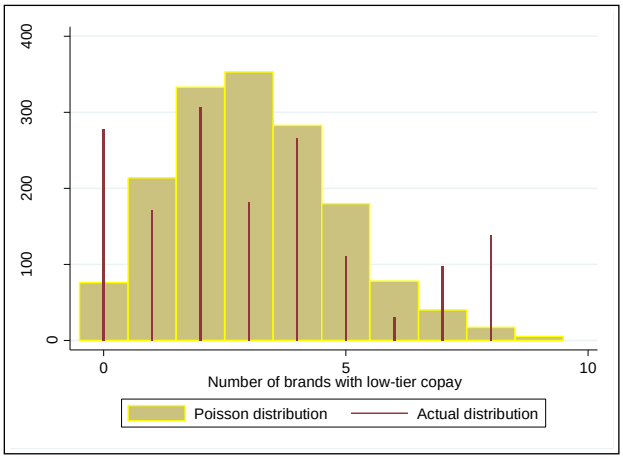
Figure 1. Histograms of numbers of on-patent drugs covered in low copay tiers (actual vs Poisson)

ARB indicates angiotensin II receptor blocker; HMG, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; PBM, pharmacy benefit management; P-TKI, protein-tyrosine kinase inhibitor.

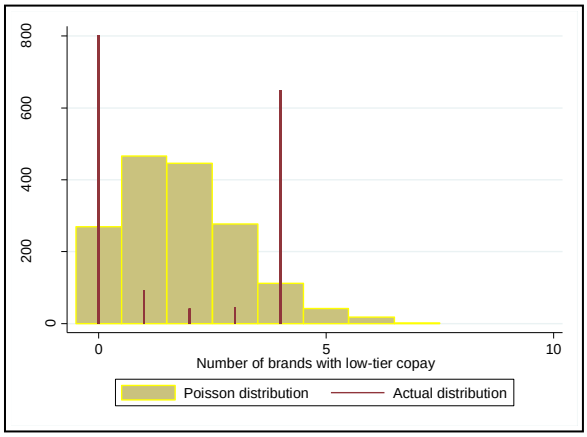
ARBs



HMGs



P-TKIs



Note: The Poisson distributions were computed by using the in-sample means of on-patent drugs in tier 1 or tier 2 (3.1 for HMGs, 2.2 for ARBs and 1.7 for P-TKIs). Over-dispersion was tested using the regression-based approach suggested by Cameron and Trivedi.[32]

Appendix 6: Plan competition variable

Plan competition was defined as a count of competitors belonging to the same category (eg, PBMs) and operating in the same state. The hypothesis to justify that choice is that the more competitors a company faces, the higher the competition. The variable was assessed in three stages. First, the number of companies operating in each state was calculated for each insurance type. Then, all states where a company was operating were identified. Finally, a company's competition value was defined as the average (across states) of the number of plans of the same insurance type.

The calculations above can be illustrated using the case of Harvard Pilgrim. Harvard Pilgrim is a commercial plan operating in four states (Massachusetts, Maine, New Hampshire and Rhode Island). There are 34 commercial plans operating in Massachusetts, 21 plans in Maine, 23 in New Hampshire and 23 in Rhode Island. Therefore, the plan competition value for Harvard Pilgrim is 25.25 (average of 34, 21, 23 and 23).

Since employees cannot choose a health insurance plan from another employer, employer plans were assumed not to compete against each other.

Societal Valuation of Fetal Deaths: A Discrete Choice Experiment.

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ABSTRACT

Many studies found that the value of a life saved varies based on the characteristics of life, such as age. However, no study has evaluated the value of avoiding fetal deaths which represent a substantial disease burden in developed and developing countries. In order to make this evaluation, 2,607 individuals over 18 years of age in the United States were surveyed online using a systematic random sampling method. A discrete choice model was designed in which respondents had to allocate a unique life-saving treatment between an unborn child, a newborn infant and a five year old child. The strength of preferences was estimated using visual analog scales. 69% of respondents preferred to allocate the life-saving treatment to a newborn infant over an unborn child in the sixth month of pregnancy. 5% chose the unborn child, 26% could not decide on which child to treat and preferred to leave the outcome to chance. 54% of respondents chose a newborn infant over an unborn child in the ninth month of pregnancy, 39% could not decide and 7% chose the unborn child. Approximately 75% of the respondents who chose the newborn found the decision difficult. The strengths of preferences for unborn children were between 46% (95% confidence interval (CI): 44%-47%) and 56% (95% CI: 55%-58%) of the level for the newborns. The preferences varied significantly by income, attitude towards religion (religious inclination), intent to have a child, previous experience with fetal loss, occupation and gender. Based on the survey results, society puts value on avoiding fetal loss albeit not as much as on preventing the death of a newborn child. The priority increased with gestational age. Therefore, the prevention of fetal deaths should be included in economic evaluations.

INTRODUCTION

Fetal death is a major health issue. 2.6 million fetal deaths are reported annually worldwide (World Health Organization, 2011). Fetal death is defined, in the United States, as a death occurring between the 20th week of pregnancy and birth (Macdorman & Kirmeyer, 2009). In the United States (US) alone, there were 26,000 fetal deaths in 2005 (Macdorman & Kirmeyer, 2009). In other words, one out of every 160 pregnancies ends in fetal death and there are as many fetal deaths as infant deaths in the US (Group, Stillbirth Collaborative Research Network Writing, 2011). The causes of fetal deaths have multiple etiologies. In developed countries, between 10% and 25% may be caused by an infection (Goldenberg & Thompson, 2003). Infections may cause fetal death through several mechanisms: (i) fetal infection (ii) severe maternal illness or (iii) placental infection (iv) precipating preterm labor with the fetus dying during labor (and delivery) (Reddy, et al., 2009). Examples of bacterial infections of the fetus include those with group B streptococcus, escherichia coli and enterococcus (Petersson, et al., 2002). Viral agents including rubella, human cytomegalovirus (CMV), parvovirus B19, herpes simplex virus (HSV), lymphocytic choriomeningitis virus (LCMV) and varicella zoster virus (VZV) may also cause intrauterine deaths (Rawlinson, et al., 2008).

Vaccines against a number of infections potentially linked to fetal death have been launched recently (e.g. VZV vaccine, group B streptococcus vaccine). If the association between infections and fetal deaths is causal, preventing infections of pregnant mothers could reduce the number of fetal deaths. In that case, vaccine manufacturers and public health officials ought to better understand how preventing fetal death is viewed by society before investing in such

vaccines. In particular, public health officials should understand whether or not an intervention able to prevent one fetal death should be rated equally to an intervention preventing the death of an infant. If the population sees the two as equal, an intervention preventing fetal deaths should be given the same priority and should be associated with the same value as an intervention avoiding infant deaths. Otherwise, the intervention should not receive the same priority.

A number of studies found that the value of life varied with the characteristics of the life to be saved (Mortimer & Segal, 2008) (Winkelhage & Diederich, 2012) (Nord, Richardson, Street, Kuhse, & Singer, 1995). In particular, age, severity of illness and behavioral causes of illness impacted the value given by society to health benefits. However, no research has been published that evaluates whether society perceives preventing fetal deaths as more, less or equally important compared to protecting infants. From a health economics perspective, new treatments are evaluated based on their abilities to maximize health benefits such as Quality Adjusted Life Years (QALY) in relation to the cost. Therefore, a treatment avoiding one fetal death and leading to one live birth should have a similar economic value as a treatment preventing one early infant death. However, the answer may not be this straightforward. Work by Erik Nord and colleagues showed that society does not necessarily value health benefits in the same way as economists (Nord, Richardson, Street, Kuhse, & Singer, 1995). In addition, the replacement child theory, which is the extent to which parents will have a child to replace a child that died, could imply that the death of an unborn child should not have the same value as that of a teenager (Zhang, 1990). Finally, Schelling's so-called identifiable victim effect may imply that people value the life of a born child with whom parents have bonded more than that of an unborn

child (Schelling, 1968). The objective of this article is to estimate the value of preventing fetal deaths by American society.

METHODS

Experimental design and survey

An online questionnaire was created and began with the following preface:

"In an ideal world, everyone would like to receive the treatment they need or deserve. Sometimes, this is not possible due to lack of money or lack of available treatments. For example, not all patients can receive vital organs (like heart or kidney) for transplant and not all patients can be treated with very expensive cancer therapies. Simply put, not all patients receive all health care they would like or deserve with some patients being given priority over others. In this study, we would like your feedback regarding the prioritization of treatments. The focus of the survey is in the area of unborn children versus those who are born. You will be asked to make choices between born and unborn children across different ages. We understand that this is a very sensitive area. Therefore, we appreciate the level of thought you put into this survey." We also clarified that the objective of the survey was not to propose or defend healthcare rationing.

Next, a hypothetical situation was set up in which a life-saving treatment could cure an unborn child in the sixth month of pregnancy or a newborn infant. The treatment could only be made available for one individual. Respondents were asked to select which of the two individuals should be given priority, or to leave the outcome to chance as to which individual would be treated. Similar to Nord and colleagues (Nord, Richardson, Street, Kuhse, & Singer, 1995), respondents were asked to rate the difficulty of the decision-making process on a 3-point scale. Different pairs of alternatives were tested to assess how the gestational age of the unborn child, the number of unborn children to be saved and the age of the born child could impact the

answers. Respondents who chose the newborn or the unborn were also asked to provide the reasons behind their choice. Finally, a visual analogue scale, in the form of a continuous sliding scale from 0 to 100 points, was used to capture the strength of the respondents' preferences. The instructions to use the scale were as follows: respondents could allocate 100 points to their choice if they believed completely that the treatment should be allocated to such individual. They could also allocate a proportion of the points to each option. For instance, if they did not strongly believe either way, they could allocate 50 points to each individual. Respondents who did not express a preference between unborn children and newborns were not presented the sliding scale and 50 points were allocated to both newborn infant and unborn child. All questions are available in the online Appendix and by clicking on this link. The order of alternatives was rotated to prevent order bias. Before entering the survey, all respondents were asked to agree on an informed consent for participation. A soft launch to 100 individuals was used to ensure that the questions were clearly understood. Furthermore, this pre-test included a question to gauge the understanding of the sliding scale. 99 individuals expressed that they understood the scale. Only 1 individual responded that he "did really not understand/ [was] not sure what moving the scale meant".

The design of the study was approved by the Sterling Institutional Review Board (Atlanta, GA, USA).

Sample

The sample was drawn from an online representative panel of 6.6 million individuals over the age of 18 years in the US who agreed to participate in surveys. The panel was created by

Survey Sampling International LLC (Shelton, CT, USA). Several individuals from the same household could potentially receive the survey but only one respondent per household was allowed to respond. A systematic random sampling method was used. The survey was conducted between November 29, 2013 and December 6, 2013. Ultimately, complete data was gathered from 2,607 respondents. In the pre-test, 63% of respondents chose the newborn. The sample size was determined to detect a 6%-change for a two-sided test between two subgroups with approximately 85% power. The calculation of the sample size also allowed for one subgroup to be two times smaller than the other subgroup. Demographic variables were collected to ensure that the sample was representative of the United States population. Those variables were age, gender, geographic location, education level, occupation, ethnicity, income and marital status. Additional variables such as religion, personal experience with fetal death, intent to have children and the number of children were expected to impact preferences and were also collected. Age, education, gender and occupation were collected for sample representativity but were also expected to potentially influence preferences (Nord, Richardson, Street, Kuhse, & Singer, 1995).

Data analysis

The distributions of the demographics of the sample were compared with the US population per the Current Population Survey (March 2012 Supplement) (US Census Bureau, 2012) using chi-square goodness of fit tests. The percentage of responses for each question was calculated. The proportions were calculated using the raw sample and a weight-adjusted sample.

The weights were used to ensure that the results were representative of the US population (see Supplementary Material for Methodology in the Appendix).

If individual *i* chooses to allocate p_i points on the sliding scale, the preference level of respondent *i* for individual of type *j* (*j*=1 for newborn infant, *j*=0 for unborn child) was defined by $p_{i,j} = \delta_{i,j} p_i + (1 - \delta_{i,j})(100 - p_i)$, where $\delta_{i,j}$=1 of individual *i* chose the alternative *j* or did not express any preference, $\delta_{i,j}$=0 otherwise. The estimated average preference across the sample for individual of type *j* is defined as P_j and was estimated by $\widehat{P_j} = \frac{1}{n}\sum_{i=1}^{n} p_{i,j}$. The 95%-confidence interval of $\widehat{P_j}$ was calculated using the mean and the variance of the sample mean assuming a normal distribution. It is trivial to show that $p_{i,0}+p_{i,1}$=100. Therefore, all individuals in the sample had the same number of points to allocate in the calculations. Similarly, P_0+P_1 =100 and, therefore, the ratio of preferences for unborn children vs. newborn (P_0/P_1) is also (100-P_1)/P_1. The confidence interval for P_0/P_1 was estimated with 2,000 draws from the distribution of $\hat{P}_1$.

Univariate analyses and multinomial logit were used to assess the impact of personal characteristics on preferences between options. Fisher's exact test or Pearson's chi-square, depending on the number of categories were used to test whether preferences varied by categorical demographics. A Kruskal Wallis test was used for the ratio variables age and number of children. Since the sample size ran into the thousands, the significance threshold used was .01 for univariate analyses. Since respondents could choose between three alternatives in each of the nine questions (i.e. an unborn child, a newborn or an equal preference), a multinomial logit model was used to assess the impact of personal characteristics on potential choices. Wald and

likelihood ratio tests were used to test the joint significance of categorical variables with more than two levels and assess whether or not variables should be included in the model. More details on the multinomial logit model can be found in the supplementary material and in the work of Andrew Jones (Jones, 2000). Finally, ordinary least squares regressions (OLS) were run to assess the impact of respondents' characteristics on the strength of their preference.

All data analyses were performed using the statistical analysis program Stata, version 12.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Survey population

The characteristics of the survey population are provided in Table 1. The descriptive statistics are presented for the raw data as well as for the weight-adjusted data. The average age of the respondents was 45.4 years (range from 18 to 92 years) and the average number of children was 1.5. The individuals with children had, on average, 2.4 children. 13 individuals had more than 10 children. After weight adjustment, 68% of the respondents were white, 12% African-American and 12% Hispanic (results not shown). When the raw data was adjusted with weights, the only groups that were under-represented by more than 2 percentage points compared to the Current Population Survey (CPS) were high school graduate or less and Hispanic. Individuals with a bachelor's degree or higher were over-represented by six percentage points even after weight adjustment.

Respondents' religious beliefs and affiliations after weight adjustment were similar to those estimated by Kosmin and Keysar (2009). 34% of the respondents were protestant, 26% were catholic, 15% had no religion or church affiliation and 3% were Jewish. 29% of the sample attended a place of worship once a week or more and 41% went more than once a month (results not shown). 33% had either personally experienced a fetal death or had a close family member who had. 53% of the individuals who personally experienced fetal deaths were women.

Average preferences and strength of preferences

When asked to allocate the life-saving treatment between a newborn infant and an unborn child in the sixth month of pregnancy, 69.0% of respondents chose the newborn infant

and 25.9% did not want to make a choice and preferred to leave the outcome to chance. Results are presented in Table 2. 5.1% of the respondents selected the unborn child. For the vast majority of respondents, making a decision was difficult. Specifically, 71.9% of the respondents who selected the newborn found the choice difficult. More specifically, 36.0% of respondents found it slightly difficult and 35.9% very difficult. If the unborn child was in the ninth month of pregnancy, 54.0% of the respondents chose the newborn and 39.1% did not want to choose. Choosing between an unborn child in the ninth month of pregnancy and a newborn was seen as more difficult than choosing between an unborn child in the sixth month of pregnancy and a newborn. 69.5% of the respondents who chose the newborn justified their choice with the perceived higher likelihood of survival. When asked to assume that the unborn child and the newborn infant had the same chance to reach adulthood, 19.8% of the respondents who chose the newborn changed their decision. Therefore, almost half of the respondents made the no-preference option the most prevalent choice. Additional reasons that the newborn was chosen were: (i) the newborn was already breathing (36.7% of responses); (ii) parents would have bonded more with a newborn than an unborn child (28.0% of responses). 81 (5.8%) respondents provided additional reasons such as risks to the mother. Some respondents assumed that the diagnosis was not accurate for an unborn child and a cure could be found by the time delivery occurred. Those assumptions increased the preference toward saving a newborn child. The reasons that the unborn child in the ninth month of pregnancy was chosen were: (i) pro-life belief; (ii)"at ninth month, the child is alive and ready to be delivered"; (iii) the assumption that the unborn child would fare better with treatment; (iv) the mother could be at risk if the unborn was not saved.

When the treatment had to be allocated between an unborn child and a five year old, between 63.8% and 73.6% of respondents chose the five year old. Choosing a five year old over an unborn child was seen as slightly less difficult than choosing a newborn over an unborn child (between 59.5% vs. 62.4% vs. between 71.9% vs. 74.9% respectively). The results imply that respondents considered saving a five year old as more important than saving a newborn. This was confirmed when respondents were asked directly to choose between these two individuals. More respondents chose the five year old (43.6%) than the newborn (10.7%). However, almost half the respondents did not want to make a choice (45.6%).

Unborn children in the sixth month of pregnancy received 31.4 points (95% confidence interval (CI): 30.5-32.2) out of 100. Unborn children in the ninth month of pregnancy received 36.0 points (95% CI: 35.1-36.8). Removing the weight-adjustment decreased the preferences of unborn children by at most 0.3 points. The average preference for unborn children in the sixth month of pregnancy was 46% (95% CI: 44%-47%) of the level of the preferences for the newborns. For unborn children in the ninth month of pregnancy, it was 56% (95% CI: 55%-57%) of the level of the preferences for the newborn.

Preferences in key demographic subgroups

Table 3 shows the association and the significance level between key demographics and stated preferences. Men were more inclined to make a decision than women when the choice was between an unborn child and a newborn. Respondents who attended a place of worship more than once a week were less inclined to make a choice ($p<0.01$ except when they had to choose between a newborn and a child in the ninth month of pregnancy). The level of income

significantly shaped preferences ($p<0.01$). The higher earners were more likely to make a choice and choose the newborn and a child of five years of age over the unborn child. The individuals planning to have a child ($p<0.001$), those who attended church once a week or more ($p<0.001$) and those who had experienced a fetal loss ($p<0.01$) were more likely to choose the unborn child. In other words, the experience of losing an unborn child influenced the responses and respondents were more likely to save the unborn child. White respondents chose, on average, the born individuals more frequently and the unborn children less frequently than other ethnic groups ($p<0.01$). The average age of the respondents who chose the newborn or the five year old was higher than those who chose the unborn child (i.e. younger adults were more inclined to choose an unborn child over a newborn than older adults). The difference ranged between 3.6 and 8.5 years depending on the question (results not shown). Responses did not vary significantly (at the 1%-level) between marital status or regions of origin for any question. Responses varied significantly by education level and occupation when the unborn was in the sixth month of pregnancy. Questions' difficulty was significantly different between people with and without a church affiliation ($p<0.001$). For instance, 45.1% of respondents with a church affiliation found that choosing between an unborn child in the sixth month of pregnancy and a newborn was very difficult. Only 30.9% of the atheists or respondents without a church affiliation felt the same way. Respondents who did not want to choose had (on average) the most children (results not shown).

Consistency between responses

1,976 (75.8%) respondents did not change their answers if the unborn child was in the sixth or ninth month of pregnancy. Overall, 140 (5.8%) of the responses were flagged by the consistency checks: 65 (2.5%) respondents did not choose between an unborn child in the sixth month of pregnancy and a newborn but chose the newborn when the alternative was an unborn child in the ninth month of pregnancy. 75 (2.9%) respondents chose the unborn child in the sixth month of pregnancy but did not choose the unborn child in the ninth month of pregnancy. The authors did not follow-up with respondents whose responses were flagged by the consistency checks.

The 140 respondents who failed the consistency checks had limited impact on the survey's overall results. When these 140 respondents' results were excluded, 73.4% chose the unborn in the sixth month of pregnancy and 24.7% did not want to make a decision (vs. 69.0% and 25.9% overall). 52.4% chose the unborn in the ninth month of pregnancy and 40.3% did not want to make a decision (vs. 54.0% and 39.1% overall). On the visual analog scale, 118 (4.5%) respondents gave more points to their non-preferred option than to their preferred option. By excluding those individuals, newborn preference scores only increased between 0.3 and 0.8 points.

Multinomial logit model and OLS

Table 4 presents the estimated coefficients from multinomial logit models assessing the choices between an unborn child and a newborn infant. The exponential value of an estimated coefficient has the direct interpretation of relative risk ratio (RRR) for a unit change in the corresponding. In other words, if a predictor variable has a negative coefficient (or a RRR below

1), an increase of one unit in the predictor reduces the probability to choose the alternative over the baseline (i.e. the no-preference response).

Consistent with the univariate results, a gender effect was found. Women were less likely to choose a newborn or an unborn infant (i.e. were more likely to choose the no-preference option) but the significance level varied between questions. The dichotomous variables that increased the probability to choose the unborn child were the intent to have a child ($p<0.01$), frequent attendance of a place of worship ($p<0.05$) and a previous fetal loss although the last variable was only significant for one out of two questions. The level of income increased the probability of choosing the newborn in relation to the no-preference option ($p<0.01$). Occupation only had a significant impact on the responses if the unborn was in the sixth month of pregnancy ($p<0.05$).

Education, region, ethnicity, the absence of religious affiliation, marital status, number of children and age had no significant impact in the overall decision-making process. The main differences between multinomial logit and univariate analyses results are that ethnicity, church affiliation and age are not significant under the multinomial logit.

Contrary to the multinomial logit model, age and the absence of religious affiliation were significant with OLS (Table 5). Previous experience with fetal death was not significant. The highest income category allocated, on average, six points less to the unborn children in the sixth month of pregnancy than the lowest income category ($p<0.001$). Atheists or respondents without a church affiliation allocated between five and four less points to unborn children than to newborn infants ($p<0.001$). Conversely, the respondents who attended a place of worship once a week allocated seven more points to the unborn children in the sixth month of pregnancy than

those who did not attend or attended a place of worship less than once a week ($p<0.001$). Respondents who intended to have a child in the future also allocated more points to the unborn children in the ninth month of pregnancy ($p<0.01$).

DISCUSSION

Preferences: A substantial proportion of respondents did not want to make a choice when asked to allocate a life-saving treatment between a newborn (or a five year old) and an unborn child. However, many respondents chose to allocate the treatment to a newborn and a five year old over an unborn child. The value of avoiding fetal loss increased with the gestational age. Respondents also chose the five year old over the newborn. Almost 20% of responses shifted away from the newborn when the respondents were asked to assume that an unborn child and the newborn had the same chance of reaching adulthood. Respondents' reasons were that a newborn was already breathing, had somewhat more right to live or had already been delivered. Respondents who did not want to make a choice often stated that only God, not they, should make such decisions. The choice to elect the newborn over an unborn child was found difficult for most respondents. The results confirmed the authors' priors that religion, gender, previous experience with fetal death, intent on having a child in the future and age have an impact on respondents' preferences. However, the number of children and education did not influence the preferences contrary to the authors' priors or comparable experiments (Nord, Richardson, Street, Kuhse, & Singer, 1995). The importance of the point of birth for the respondents was high. More specifically, the fact that a newborn is breathing (first reason given by respondents to choose the newborn in the Results section) was likely very important to the respondents.

Weights impact on the preferences: Using the raw data instead of weighted preferences had little impact on preferences. On average, they changed by 0.5 percentage point with a maximum of 1.3 percentage points (results not shown) because the sample was fairly

representative of the population. In addition, some variables used to calculate the weights (regions, marital status and education) did not have a significant impact on the responses. The fact that the results are consistent with and without weights and across methodologies is an indication of robustness of the results.

Limitations: The research could suffer from sample selection since respondents were part of a panel and had already agreed to participate in surveys. In the data analysis section, the method for addressing non-response and sample selection bias was described. However, the methodology used may not solve the problem if the selected demographics do not explain why potential respondents did not respond. Even if it was the case, representation issues could still be present since the sampled respondents had access to the internet and may be more tech-savvy than the average population. Indeed, 74% of American households had access to internet in 2010 (US Department of Commerce, 2010). Therefore, the survey may not be able to provide insight on the remaining 26%. Börsch-Supan and colleagues proposed an approach to address this bias by conducting an offline survey in addition to the online survey (Börsch-Supan, et al., 2006). For cost reasons, such an approach was not undertaken. Another limitation is that fetal diagnostics is difficult and respondents might think that an unborn with a disease has further complications.

Comparison with published literature: The results regarding the allocation of treatment between a newborn infant and a five year old were consistent with the work of Nord and colleagues (Nord, Richardson, Street, Kuhse, & Singer, 1995). In that article, respondents in Australia had to give one organ to either a young child or a newborn infant. Respondents could also choose a no-preference answer. 44% of the Australian and the American respondents favored the child. In Australia, slightly more respondents chose the no-preference option (55%

vs. 46% in the US) and one percent chose the newborn vs. 11% in the US. 71% of the American and Australian respondents who chose the newborn found that the decision was difficult. Felder and colleagues (2003) also found that the prospect of a healthy child had more influence than saving an unborn child. More specifically, they showed that a medical board that recommended routine amniocentesis for women older than 35 valued the detection of a fetus with chromosomal anomaly about six times higher than the loss of an unaffected fetus (Felder, Werblow, & Robra, 2003). It should be noted that this ratio is higher than in our study and medical boards, not society, were in charge of making such decisions.

Implication for health economics evaluations: Society puts substantial value into avoiding fetal death albeit not as much as into preventing the death of a newborn child. As such, the prevention of fetal death should be considered in economic evaluations. This conclusion comes from the high number of respondents who did not want to make a choice, the perceived difficulties of the choice and the relative strengths of preferences. Different approaches are possible to include the prevention of fetal death in economic evaluations. Life years saved or QALYs saved by preventing a fetal death could be considered similarly to the evaluation of the prevention of the death of newborns: the differences in preferences between an unborn in the ninth month of pregnancy and a newborn were comparable (although slightly more pronounced) to those between a newborn and a five year old, and, therefore, similar weights should be used for unborn children. Alternatively, the QALYs used for an unborn child may be of lower value than those of a newborn since society, based on this survey, puts more emphasis into saving a newborn. The value to be applied could be the relative preference ratios calculated in this article. If such approach were to be used, the QALYs to account for the loss of an unborn child should

be between 0.44 and 0.58 times that of a newborn infant. The value could vary by gestational age. However, the solution may not reside purely in the conclusions drawn from this survey. Respondents made a number of assumptions when answering the questionnaire (e.g. on the likelihood of an unborn child reaching adulthood) and may not be fully informed about the impact of losing an unborn child (hence the differences in preferences between those who experienced this loss and those who did not). Before making a decision, additional studies should be conducted to better understand the consequences for parents' quality of life following the death of a child at different life stages. These studies would allow policy makers to weigh the responses in this survey. Alternatively, the number of live births could be used as a valid endpoint in clinical trials for interventions preventing fetal deaths. This approach would address the issues expressed by respondents that unborn children had a lower chance of survival than newborns.

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Table 7: Descriptive statistics of the survey sample. Data are shown as number (%)

	Raw Sample (N=2,607)	Weight-adjusted sample	US census (age≥18 years)
Age			
18-24 yrs	13%	14%	13%
25-34 yrs	19%	19%	18%
35-44 yrs	17%	17%	17%
45-54 yrs	19%	18%	19%
55-64 yrs	16%	16%	16%
>=65 yrs	16%	17%	18%
Average age	45.4	45.4	
Male	48%	49%	48%
Educational level			
Less than high school graduate	3%	10%	13%
High school graduate or GED	22%	27%	30%
Some college or associate degree	37%	29%	29%
Bachelor's degree or higher	38%	34%	28%
Household income per year			
Under $20,000	17%	14%	14%
$20,000 to $39,999	25%	20%	19%
$40,000 to $59,999	22%	17%	17%

$60,000 to $99,999	22%	24%	24%
$100,000+	14%	26%	26%
Occupation			
Employed	51%	59%	59%
Unemployed	10%	6%	6%
Not in labor force (retired, student, household duties…)	39%	35%	35%
Religion			
Protestant (evangelical and non-evangelical)	34%	33%	
Catholic	24%	26%	
No religion/ no church affiliation	16%	15%	
Atheist/ Do not believe in God	4%	4%	
Prefer not to say	5%	4%	
Other	18%	19%	
Number of children in household	1.5	1.6	
Intent on having a child in the future	23%	25%	
Loss of unborn child			
No	68%	66%	
Yes, I have	13%	14%	

Yes, close family member has	19%	19%

Note: Ethnicity, region, marital status, church/temple attendance are not shown.

Table 2: Weight-adjusted preferences and difficulty of choice

Question	Choice	% choosing the option	Difficulty of choice (%)		
			Not difficult	Slightly difficult	Very difficult
6m vs. newborn	Equal priority	25.9	17.8	25.5	56.8
	Favor newborn	69.0	28.1	36.0	35.9
	Favor unborn	5.1	18.2	52.5	29.3
9m vs. newborn	Equal priority	39.1	14.8	25.3	59.9
	Favor newborn	54.0	25.1	34.4	40.5
	Favor unborn	6.9	16.9	49.3	33.8
6m vs. child of 5-yr	Equal priority	21.4	16.4	28.6	55.0
	Favor child	73.6	40.5	28.6	30.9
	Favor unborn	5.0	21.4	40.7	37.9
9m vs. child of 5-yr	Equal priority	29.3	16.2	26.4	57.4
	Favor child	63.8	37.6	27.9	34.5

	Favor unborn	6.9	25.8	38.0	36.2
Newborn vs	Equal priority	45.6	11.8	22.5	65.7
child of 5-yr	Favor child	43.6	28.8	27.9	43.3
	Favor newborn	10.7	20.8	39.2	40.0

Table 3: Summary of the univariate analyses

		6m vs. newborn			9m vs. newborn			6m vs.child of 5 years			9m vs. child of 5 years		
Variable	Level	No preference	Un-born	p-value	No preference	Un-born	p-value	No preference	Un-born	p-value	No preference	Un-born	p-value
Gender	Male	25.1	6.7	0.00	34.3	8.1	0.00	22.6	5.4	0.14	27.8	8.2	0.03
	Female	29.0	3.0		43.7	4.5		22.3	3.8		30.2	5.8	
Child intent	No	27.1	3.6	0.00	38.4	4.5	0.00	21.7	3.2	0.00	27.9	5.7	0.00
	Yes	27.3	8.6		41.8	11.8		24.8	9.0		33.1	11.2	
Atheist/ no religion	No	27.9	5.3	0.01	39.8	6.8	0.01	23.0	5.1	0.01	30.2	7.2	0.01
	Yes	24.2	2.5		36.7	3.8		20.2	2.5		24.8	5.8	
Church≥ 1x/week	No	25.7	3.2	0.00	38.3	5.0	0.00	20.7	3	0.00	27.1	5.5	0.00
	Yes	31.0	8.9		41.7	9.3		26.9	8.6		34.2	10.7	
Fetal loss experience	No	27.2	4.1	0.00	38.7	5.6	0.00	22	4	0.00	28.2	6.4	0.00
	Yes	26.9	9.5		42.6	10.4		25.1	8.6		35.2	10.7	
Income	<$20k	35.1	6.5	0.00	45.9	7.9	0.00	29.3	6.1	0.00	34.7	9.5	0.00
	$20.0-$39.9k	27.8	3.6		39.9	4.5		24.2	3.8		30.1	6.0	
	$40.0-$59.9k	28.0	6.3		38.3	6.8		24.3	5.1		30.4	8.0	
	$60.0-$99.9k	25.0	2.7		37.4	6.8		18.4	4.5		25.7	6.4	
	>$100.0k	18.0	5.4		33.8	5.4		14.1	3.4		23.4	4.5	
Ethnicity	White	26.3	3.9	0.00	38.7	5.3	0.01	20.8	4	0.00	27.8	6.1	0.00
	Black	28.7	8.6		44.7	7.8		29.5	6.1		35.7	8.6	

Asian/Other	34.4	5.4	40.3	7.5	29.6	5.9	29.6	10.8
Hispanic	27.2	7.5	36.4	11.0	22.8	7.0	32.9	9.6

Table 4: Multinomial logit model predicting the preferences (no preference is baseline)

	Unborn (6th month pregnancy) vs. newborn		**Unborn (9th month pregnancy) vs. newborn**	
	Newborn	Unborn	Newborn	Unborn
Female	-0.14	-0.91***	-0.33***	-0.82***
Income (reference="less than $20,000")	.	.	.	
$20,000 to $39,999	0.37**	-0.37	0.33*	-0.42
$40,000 to $59,999	0.30*	0.07	0.34*	-0.02
$60,000 to $99,999	0.55***	-0.82*	0.41**	-0.05
$100,000+	0.93***	0.17	0.56***	-0.22
Occupation (reference=employed)	.	.	.	
Unemployed	-0.28	0.26	-0.12	0.27
Not in labor force (retired, student, household duties…)	0.12	-0.21	0.07	-0.004
Church≥1x/week	-0.42***	0.74***	-0.24*	0.39*
Experienced an unbornloss	-0.02	0.66**	-0.19	0.31
Child intent	-0.03	0.70**	0.23*	0.83***
Constant	0.71***	-1.78**	-0.32*	.-1.82***
Observations	2607		2607	
AIC	3848		4456	

legend: * p<0.05; ** p<0.01; *** p<0.001

Table 5: Strength of preferences for unborn children (OLS results)

	Impact on allocated points	
	(6^{th} month pregnancy)	(9^{th} month pregnancy)
Age	-0.13***	0.10**
Female	0.66	2.24*
Income (reference="less than $20,000")	.	.
$20,000 to $39,999	-3.42*	-2.95*
$40,000 to $59,999	-3.35*	-2.14
$60,000 to $99,999	-5.88***	-2.64
$100,000+	-6.02***	-4.39**
Occupation (reference=employed)	.	.
Unemployed	3.01	2.08
Not in labor force (retired, student, household duties…)	-1.18	-0.63
Church≥ 1x/week	6.70***	4.16***
Fetal loss experience	0.73	1.89
Child intent	2.24	3.08**
No religion/atheist	-4.56***	-3.89***
Constant	39.07***	40.14***
Observations	2607	2607
AIC	23447	23431

legend: * p<0.05; ** p<0.01; *** p<0.001

The table above presents the regression coefficients of key covariates on the number of points (out of 100) allocated to unborn individuals

Appendix: Questionnaire

Question 1. Imagine two individuals have a disease that leads to death if not treated. One is an **UNBORN CHILD** in the **SIXTH month of PREGNANCY**. The other is a **NEWBORN INFANT**. A treatment to cure this disease exists but can only be produced for **ONE** individual.

- The **NEWBORN INFANT** should receive the treatment
- Either. Will leave it to chance as to which one is treated
- The **UNBORN CHILD** (6^{th} month pregnancy) should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult
- Not difficult

Question 2. Imagine two individuals have a disease that leads to death if not treated. One is an **UNBORN CHILD** in the **NINTH month of PREGNANCY**. The other is a **NEWBORN INFANT**. A treatment to cure this disease exists but can only be produced for **ONE** individual.

- The **UNBORN CHILD** (9^{th} month pregnancy) should receive the treatment
- Either. Will leave it to chance as to which one is treated
- The **NEWBORN INFANT** should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult

- Not difficult

Question 3 (if answer to question 2a was "The NEWBORN INFANT should receive the treatment").

People may have different reasons for making this choice. Which of the following made you select the **NEWBORN INFANT** over the **UNBORN CHILD**? ((You may select more than one)

- The NEWBORN INFANT has a higher chance to survive and reach adulthood than the UNBORN CHILD, for instance, the UNBORN CHILD may not survive delivery
- A child who is born has more right to receive treatment than a child that hasn't been born
- Parents will have bonded with a NEWBORN INFANT to a greater extent than with an UNBORN CHILD
- The NEWBORN INFANT is already breathing
- Other (Please specify)

Question 3b (if answer to question 2a was "The UNBORN CHILD should receive the treatment").

People may have different reasons for making this choice. Which of the following made you select the **UNBORN CHILD** over the **NEWBORN INFANT**?

- Other (Please specify)

Question 4. Please assume that the **UNBORN CHILD who has entered the NINTH month of PREGNANCY** and the **NEWBORN INFANT** will reach adulthood in perfect health if they receive the treatment. A treatment to cure this disease exists but can only be produced for **ONE** individual.

If only one individual can be treated, which of the following do you agree with?

- The **UNBORN CHILD** (9^{th} month pregnancy) should receive the treatment
- Either. Will leave it to chance as to which <u>one</u> is treated
- The **NEWBORN INFANT** should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult
- Not difficult

<u>Question 5</u>. Imagine two individuals have a disease that leads to death if not treated. One is an **UNBORN CHILD** in the **SIXTH month of PREGNANCY**. The other individual is a **child of 5 YEARS of AGE**. A treatment to cure this disease exists but can only be produced for **ONE** individual.

a. If only one individual can be treated, which of the following do you agree with?

- The **CHILD of 5 YEARS of AGE** should receive the treatment
- Either. Will leave it to chance as to which <u>one</u> is treated
- The **UNBORN CHILD** (6^{th} month pregnancy) should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult
- Not difficult

<u>Question 6</u>. Imagine two individuals have a disease that leads to death if not treated. One is an

UNBORN CHILD who has entered the **NINTH month of PREGNANCY**. The other individual is a **child of 5 YEARS of AGE**. A treatment to cure this disease exists but can only be produced for **ONE** individual.

a. If only one individual can be treated, which of the following do you agree with?

- The **UNBORN CHILD** (9^{th} month pregnancy) should receive the treatment
- Either. Will leave it to chance as to which one is treated
- The **CHILD of 5 YEARS of AGE** should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult
- Not difficult

Question 7. Imagine two individuals have a disease that leads to death if not treated. One is a **NEWBORN** and the other individual is a **child of 5 YEARS of AGE**. A treatment to cure this disease exists but can only be produced for **ONE** individual.

a. Which of the following do you agree with?

- **The CHILD of 5 YEARS of AGE** should receive the treatment
- Either. Will leave it to chance as to which one is treated
- The **NEWBORN INFANT** should receive the treatment

b. Did you find that making this choice was?

- Very difficult
- Slightly difficult

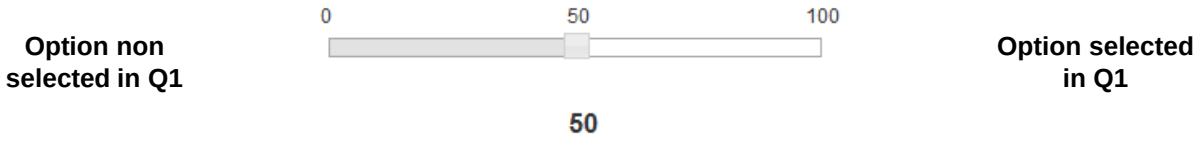
- Not difficult

Question 8 (if the NEWBORN or the UNBORN CHILD was selected in Q1). In a previous question, you chose to allocate the treatment to < *Q1 answer*> when the treatment was available to treat an UNBORN CHILD in the SIXTH month of PREGNANCY OR a NEWBORN INFANT.

Could you please show us by using the slider below how strongly you believe that this should be the case using a scale from 0-100 points. If you believe this completely, then you may wish to allocate all 100 of the points to that end of the scale. However, you may wish to allocate a proportion of the points to each option.

For instance, if you did not strongly believe either way, you may wish to allocate 50 points

Moving the slider will automatically show you how many points you have allocated to each option.



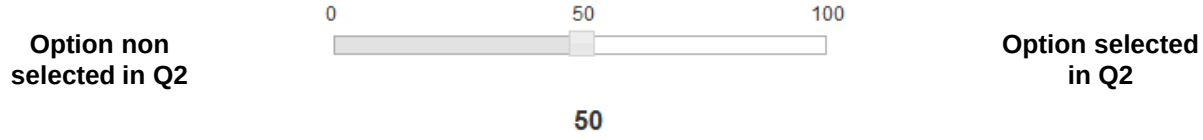
Question 9 (if the NEWBORN or the UNBORN CHILD was selected in Q2). In a previous question, you chose to allocate the treatment to < *Q2 answer*> when the treatment was available to treat an UNBORN CHILD in the NINTH month of PREGNANCY or a NEWBORN INFANT.

Could you please show us by using the slider below how strongly you believe that this should be the case using a scale from 0-100 points. If you believe this completely, then you may wish to allocate

all 100 of the points to that end of the scale.

However, you may wish to allocate a proportion of the points to each option. For instance, if you did not strongly believe either way, you may wish to allocate 50 points.

Moving the slider will automatically show you how many points you have allocated to each option.



Supplementary material - Methods

Sample weights calculation

The weights were used to ensure that the results were representative of the US population. Weights were calculated with a logistic regression-based solution that appended the survey and CPS datasets[14]. The logistic regression used the variables available both in the survey and in the census data, namely age, region, gender, education, occupation, ethnicity, household income and marital status. The dependent variable was equal to 1 if an observation was part of the survey datase and 0 if the observation was part of the CPS dataset[14]. Therefore, the predicted probability for each observation corresponded to the probability of the observation to be part of the survey given his/her demographic. By definition, the sampling weight was the inverse of the predicted probability.

Multinomial logit

Let the indirect utility of alternative j (j=0, 1, 2) for invidividual i be $V_{ij}=z'_i\alpha_j+\varepsilon_{ij}$ with z_i being a vector of characteristics that varies across individuals but not across choices, and α_j being a vector varying across choices and not across individuals, and ε_{ij} of type I extreme value. The multinomial logit model can be derived from the random utility model if the ε_{ij}'s are independent. The probability that individual i chooses the alternative j is defined by:

$$P_{ij} = \frac{\exp(z'_i\alpha_j)}{\sum_{k=0}^{k=2}\exp(z'_i\alpha_k)}$$

The relative probabily that an individual i chooses alterntive j over k is:

$$\frac{P_{ij}}{P_{ik}} = \frac{\exp(z'_i\alpha_j)}{\exp(z'_i\alpha_k)}$$

The coefficients from the multinomial logit models indicate how changing the predictor value by one unit affect the probability of selecting an alternative choice relative to a reference choice. The tests of significance were conducted across all potential choices, for unborn vs. no-choice and for newborn vs. no-choice. A model approach was taken for the univariate analyses and multinomial regressions. Therefore, weights were not included in the univariate or multinomial analyses.

What is the Value of Me-Too Drugs?

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Abstract

The objective of this article is to estimate the value of 'follow-on' or 'me-too' drugs from the payer, industry and societal perspectives. Since me-too drugs do not bring additional clinical benefits, they are only valuable to payers if they save costs. An empirical model was constructed to identify the factors affecting whether a me-too drug results in cost savings to the pharmaceutical budgets of payers. These factors included the intensity of promotional spending, price discount and time to entry. Twenty-seven second-entrant products with limited differentiation were identified; their launch dates ranged from 1988 and 2009. On average, me-too drugs launch 2.5 years after the first entrant, with 20% more promotional investment, and capture 38% of market share within 4 years. Peak market share is significantly affected by share of voice ($p<0.001$) but not price discount ($p=0.77$). Launch delay was significant in terms of reducing both market share ($p<0.001$) and price ($p<0.05$). With a launch price 15% below the incumbent, cumulative savings from use of a me-too drug peak at over $1000 million, but decrease rapidly after the first entrant becomes generic and only amount to $450 million over the me-too drug's lifecycle. With a price discount less than 10%, cumulative savings are negative over the life of the me-too drug. Therefore, me-too drugs may be cost saving in the short term, but can represent a cost in the longer term. From a societal perspective, me-too drugs always decrease the economic surplus if they do not grow the market. If me-too drugs grow the market by 20%, they augment, on average, the economic surplus only if the variable costs (including promotional investment) do not increase by more than $300 million per year.

***Key Words**: follow-on drugs, cost savings, peak share, share of voice, first-mover advantage*

MSC codes: 62J05, 62P20, 90B50

1. Introduction

Over recent decades, numerous new treatments have been developed for diverse medical conditions such as hypertension, hypercholesterolemia, cancer and HIV. Between 1990 and 2004, 431 new molecular entities were approved by the US Food and Drug Administration (FDA) [1]. Some compounds were genuine innovations, while others provided limited incremental therapeutic value over existing products. The former are often referred to as 'breakthrough' drugs, 'first-in-class' or 'innovators', while the latter are called 'incrementally modified' drugs, 'follow-on' drugs or, more often, 'me-too' drugs. In fact, the FDA assessed that 183 (42%) of the 431 new molecular entities were "significant improvement[s] compared to marketed products" and the remaining 248 (58%) appeared to "have therapeutic qualities similar to those of one or more already marketed" [1].

Given their limited incremental clinical benefits and their number, understanding the value of me-too drugs is critical for pharmaceutical companies when making research and development (R&D) decisions. As development costs can reach approximately $800 million per drug, pharmaceutical companies must often make trade-off decisions in their R&D portfolios [2]. Forecasting the potential of me-too drugs is important for informing resource-allocation decisions. Understanding the value of such drugs is also critical for payers (e.g. health insurers) when making reimbursement decisions; for physicians and patients when electing treatment choice and allocating healthcare spending; and for society when improving efficiency by directing healthcare resources to the most cost-effective uses.

1.1. Background

Me-too drugs lack innovation compared with existing therapeutic options and have been widely criticised in the general press [3] and the scientific literature on a number of grounds.

For example, it has been argued that they divert R&D investment away from diseases with higher unmet needs [4] and may even damage innovation by reducing incentives to pioneer new therapeutic classes because me-too drugs curb the innovator's profits [5]. Pharmaceutical companies have been criticised for increasing spending on direct-to-consumer (DTC) advertising of me-too drugs, which has been perceived as tending to promote drugs over a healthy lifestyle and may lead to overconsumption [6]. Follow-on drugs may also limit the penetration of generics after the first-in-class drug is no longer protected by patent [7]. Me-too drugs can significantly augment expenditure growth. 80% of the increase in drug expenditures between 1996 and 2003 in British Columbia could be explained by the use of drugs without clinical benefits over older drugs, most of which had lost patent [8].

Although increased competition from me-too drugs might be expected to lead to a decrease in price, this has not always occurred, which has led to criticism of the drug companies [9]. Azoulay found that in the histamine H_2-receptor antagonist market, Tagamet's price increased when Zantac, its first competitor, entered the market [10]. Additionally, Tagamet and Zantac prices continued to increase when other competitors were launched [10]. However, this study failed to account for the fact that potentially a higher price increase might have occurred without any new competition.

Conversely, it can be argued that me-too drugs have numerous positive effects. For example, they may provide improvements (albeit marginal) in treatment for some patients; there is evidence that for some diseases, patients do in fact respond differently to me-too drugs. For instance, although numerous randomized trials showed no significant differences in clinical effectiveness between selective serotonin reuptake inhibitor (SSRI) antidepressants, more than half of the patients who do not respond to one SSRI antidepressant benefit from another drug in the same class [11]. Notwithstanding the example of the H_2-receptor antagonist drugs discussed above, me-too drugs are typically introduced at a discount in the US and

subsequent price increases are lower when there are more branded substitutes in the market [12]. Lexchin (2006) analysed 33 new me-too drugs in Canada and found that the mean introductory price was 8.5% lower than the price of the most expensive brands [13]. Furthermore, payers are likely to use new entrants as a means to extract better value from the class via formulary management tools. For example, in a survey conducted in the USA most health plans stated that they would demand a 20% discount compared with Advair to grant Dulera a favourable formulary position [14].

Although the name 'me-too' implies imitation, the existence of me-too drugs is more often due to parallel development [15]. Parallel development may stimulate competition to become the first company to launch a breakthrough product; this, in turn, could potentially accelerate development times and enhance product profiles [16]. Me-too drugs may also augment disease awareness through increased promotion such as DTC advertising. Such an increase in awareness may increase diagnosis rates, improve compliance and lead to better health outcomes. In addition, by affecting the first entrants' profits, the introduction of me-too drugs could potentially force innovators to invest more heavily in R&D to preserve revenue and profit growth. Although it has been argued that the development of me-too drugs diverts R&D investment away from diseases with higher unmet needs [4], it can also be argued that me-too drugs generate profits for manufacturers that can then be reinvested in R&D for disease states with high unmet needs.

Given the wide range of opinions regarding me-too drugs, an objective analysis of their impact is warranted. An analysis was conducted of the impact of me-too drugs across a wide range of therapeutic areas from the perspectives of pharmaceutical companies, payers and society. A me-too drug can offer cost savings to payers if introduced at a discount but can also increase costs if it has a higher price than the generic products once the pioneer loses the patent. The key objective of this paper is to identify whether the cost savings generated from

a lower introductory price exceed the extra costs due to the slower adoption of generics after the pioneer loses patent. Additionally, the impact of me-too drugs on economic surplus is assessed.

In the next Section, the factors influencing the success and potential cost-savings of me-too drugs will be reviewed. Next, the data and the model used in the analysis will be explained and validated. Finally, the impact for payers, the pharmaceutical industry and society will be discussed.

2. Methods

2.1. Factors Influencing the Success of (Me-Too) Drugs

Marketing literature has long identified that order of entry and quality of new products impact market success [17], [18]. Fischer and colleagues (2010) analysed the sales of pharmaceutical drugs and showed that a drug's quality increases peak sales and its order of entry reduces peak sales [19]. They also showed that a firm's own market expenditures positively impact sales while price had no impact. The impact of competitive marketing expenses is mixed in the literature. Prins and Verhoef (2007) found that promotional investment spent by competitors reduces time-to-adoption [20] while Fischer and Albers (2010) [21] estimated that competitive marketing investments may have a category building effect and increase the sales of all brands in the market.

In this article, any given firm's expenditures and competitive expenditures are combined to calculate shares of promotional investment. Quality was not a relevant variable since it is similar between me-too drugs and innovators. The delay between launch of the innovator molecule and that of the me-too drug was used instead of order of entry. Additional factors considered were the duration of patent protection, price and the influence of managed care organisations.

2.2. Data Sources

A number of governmental and proprietary datasets were used for the analysis, including:

1. Product evaluations by the Transparency Commission of the French national health authority – Haute Autorité de la Santé (HAS) [22];
2. US National Prescription Audit by Intercontinental Marketing Services (IMS), which measures the flow of prescriptions dispensed by pharmacies [23];
3. Promotional audit data for the USA from SDI Health, which tracks physician/nurse detailing, meetings and events, DTC advertising, and advertising in professional medical journals [24];
4. First Databank's National Drug Data File, which provides wholesaler acquisition costs (WACs) for the USA, also called ex-factory price [25]. The WAC is the list price paid by wholesalers or distributors to manufacturers before any discounts, rebates or allowances.

2.3. Model Framework

2.3.1. Product Selection

The order of market entry and level of differentiation were estimated for the major products manufactured by the largest pharmaceutical companies (Pfizer, Johnson & Johnson, Roche, Novartis, GlaxoSmithKline, Sanofi, AstraZeneca, Abbott Laboratories, Merck & Co., Bristol-Myers Squibb, Eli Lilly, Boehringer Ingelheim, Amgen, Genentech, NovoNordisk, Bayer,Takeda, Astellas, Daiichi Sankyo) using 2007, 2008 and 2009 annual reports. The annual reports provided information for products launched as far back as 1991. To avoid selection bias (namely only screening the most successful products of the major companies),

all new molecular entities approved by the FDA from 1999[1] to 2007 were also analysed [26]. The dependent variable was the peak share over the first 4 years and recent launches could not be included. Finally, the branded versions of linisopril (Privinil and Zestril) were included in the sample since both brands were clinically undifferentiated. In the base model, Prinivil was the me-too of Zestril. In the Section 3.2., Zestril was the me-too of Prinivil. The analysis was limited to second-to-market drugs available in the USA.

Product differentiation was assessed based on Amélioration du Service Médical Rendu (ASMR; evaluation of therapeutic benefit) ratings used by the French Transparency Commission [22]. These ratings are an objective measure of the product's medical added value versus existing comparators, classified in five categories: ASMR I (therapeutic breakthrough), ASMR II (important improvement in terms of efficacy or safety), ASMR III (modest improvement in terms of efficacy or safety), ASMR IV (minor improvement in terms of efficacy or safety) and ASMR V (no improvement). The French ASMR is not the only system that evaluates drugs by assigning a rating. For instance, the German IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) rating system also attempts to establish qualitative assessments of incremental value. The French rating system has several advantages. Firstly, all products in the sample had an ASMR rating at launch [27]. This is not the case with the German system since IQWiG was founded in 2004. Furthermore, French ratings are specifically designed to inform reimbursement and pricing decisions. Finally, they provide more information than the FDA ratings which are only distributed among 3 categories (priority review, standard review, orphan designation). In Section 4.5., the impact of using the FDA instead of the HAS ratings is analysed.

[1]1999 was chosen for convenience because the FDA web site does not provide electronic annual approval files before that date.

A product was classified as a me-too drug if it belonged to the same therapeutic class as a previous entrant and if its ASMR rating was IV or V. A second entrant was also classified as a me-too drug if it had the same ASMR rating as the first entrant when compared with an alternative therapeutic class (i.e. the first and second entrants were deemed to provide the same medical improvement vs an alternative therapy). In rare instances, products with a high ASMR rating were not considered to be me-too drugs if the market's perception differed widely from that of the HAS. Thus, Lyrica, Afinitor and Valtrex were not classified as me-too drugs for this analysis. In addition, a few me-too drugs (Lunesta, Effient) were launched shortly before the first entrant's generics and were therefore excluded from the analysis. Finally, drugs dispensed via hospitals or specialty pharmacies, or which are administered intravenously in physicians' offices, were not included in the analysis as prescription information is not reliable for them. This data limitation excludes most hospital, oncology and biologic drugs from the analysis.

2.3.2. Price discount

Price discounts of me-to drugs at launch were estimated based on WACs in the USA [25].

2.3.3. Promotional investment

The share of voice (SoV) at launch was calculated. The SoV was defined as the relative portion of promotional investment of the new entrant within the two-product market composed of the incumbent and the me-too drug, according to the equation:

$$SoV_i = I_i / (I_i + I_j)$$

where SoV_i is the SoV of me-too drug i; I_i is the promotional investment (including resources spent on physician/nurse detailing, journals, events and DTC advertising) spent on me-too drug i over the first 12 months; and I_j is the promotional investment in the innovator drug j over the same period. A period of 12 months was chosen since Corstjens and colleagues

(2005) showed that the sales performance over the first 4 quarters determines 81% of the variance in sales in the long term [28]. The impact of the second year's promotional investment is estimated in the Section 3.3.

2.3.4. Market Share

The number of prescriptions (TRx) was used to calculate monthly market share, which was defined as:

$$MS_{i,t} = TRx_{i,t} / (TRx_{i,t} + TRx_{j,t})$$

where $MS_{i,t}$ is the market share of me-too drug *i* during month *t*; $TRx_{i,t}$ is the number of prescriptions filled for me-too drug *i* during month *t*; and $TRx_{j,t}$ is the number of prescriptions of the innovator drug *j* during month *t*.

Since products have different adoption patterns and the time to reach their full potential varies, peak share was used for the analysis rather than the share per time period. As multiple events occur within the product's lifetime (such as new indications), peak share was calculated over the first 4 years of sales; therefore, peak share was defined as:

$$\underset{t \leq 48m}{Max}\ MS_{i,t}$$

Different calculations were used in two particular cases: (1) average share over 4 years was used for products launched in the same quarter (e.g. Actos/Avandia; Zestril/Prinivil); (2) TRx for the first 4 years were not available for Zyrtec/Allegra, so share at 5 years was used.

2.3.5. Delay in Launch of Me-too Drugs

The delay was expressed in quarters and capped at 15 quarters. The validation of this assumption is discussed in Section 2.6.

2.4. Core Methodology

Cumulative savings for payers generated by me-too drugs were assessed using the equation:

$$C_i = \sum_t D_i * P_j * Share_{i,t} * MktTRx_{i,t} \quad \textbf{[1]}$$

where $Share_{i,t}$ is the share of me-too drug *i* during the period *t*; $MktTRx_{i,t}$ is the TRx in product *i*'s market during the period *t;* P_j is the price of innovator *j*; and D_i is the price of me-too *i* relative to the innovator calculated as:

$$D_i = (P_i - P_i) / P_j$$

To estimate $Share_i$, the following regression was run:

$$Share_i = \alpha + \beta * \ln(1 + SoV_i) + \gamma * T_i + \varepsilon_i \quad \text{with } \varepsilon_i \sim N(0,\sigma^2) \quad \textbf{[2]}$$

where SoV_i is the share of voice of me-too *i* at launch; T_i is the launch delay between product *i* and the innovator drug, and ε_i is the unobserved error term. Running the regression based on share (rather than actual prescriptions) avoids overweighting markets with high prescription volume. A logarithmic function for promotion was used because a decreasing return on promotion was expected.

To estimate price D_i, the following model was used:

$$D_i = D_0 + \lambda * T_i + \varepsilon'_i \quad \text{with } \varepsilon'_i \sim N(0,\sigma'^2) \quad \textbf{[3]}$$

where D_i is the price of product *i* at launch, relative to the innovator drug and ε'_i is the unobserved error term. Note that, over time, the relative price level may not remain constant. In particular, first and second entrants are unlikely to increase prices at exactly the same time. However, choosing to apply the discount at launch simplifies the analysis and the interpretation of the results.

The share and the price models could have been run concomitantly (using equation [1]). However, equation [2] was evaluated independently because the price is set before the peak

market share is known. The impact of price on peak-share potential was analysed in the market-share model specification.

Regressions were run using the statistical analysis programs Stata (StataCorp LP, College Station, TX, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

2.5. Model Validation

As the models rely on least-square estimates with a small number of observations, the following tests were used to ensure ordinary least-square assumptions for finite samples were not violated: (1) White test (homoscedasticity); (2) Ramsey RESET test (functional form of the conditional mean); (3) Shapiro–Wilk *W* test (normality of residuals); (4) variance inflation factor (absence of multicollinearity); (5) residuals versus predicted value plot (exogeneity).

2.6. Market-Share Model Specification

A number of variables were added to the model, including the impact of price discounts and a comparison of the impact of SoV in the first and second years. It is conceivable that the longer a second entrant is delayed, the more important the SoV is in driving market share. Therefore, an interaction variable between launch delay and ln(1+SoV) was introduced to test this hypothesis. An annual trend variable was included to elucidate whether the environment became more or less favourable for the me-too drugs over time.

In the core model, the impact of delay on market share was assumed to be a linear function when the launch delay was 15 quarters or less and was capped if the delay exceeded 15 quarters. With this assumption, once a certain level of delay was reached, an additional delay would not have a material impact on the potential of the me-too drug. A penalised spline regression was used to justify this assumption (data not shown).

2.7. Payer's Perspective

The cost savings of me-too drugs as a function of price discount, launch timing and SoV were modelled in a market behaving similarly to the average market in the sample: TRx potential of approximately 6 million per quarter, innovator's WAC per TRx at $150 (median WAC/TRx for the sample was $133 and average price was $170 as of December 2009). The second entrant was assumed to launch with an average SoV derived from the sample. The launch delay (10 quarters) was also derived from the sample. Given the uncertainties regarding price discounts (see Discussion), three price-discount levels were assumed for the second entrant: 5% (similar to the average in the sample), 10% and 15%. Peak shares for all scenarios were estimated from the analysis described above.

Based on the sample, the first and second entrants were assumed to have become generic after 13 years on the market. Generic exclusivity was assumed to last for 6 months. After that, multiple generic products were assumed to have been launched. Generic versions of the first entrant were assumed to capture 95% of the first entrant's TRx within a year (based on the generics' uptake of Zocor, Prilosec, Claritin and Flonase) but were assumed not to take market share away from the me-too drug. The final assumption reflects the historical lack of impact of generics on the non-generic brands [29].

During the generic exclusivity period (180 days), generic prices were assumed to be 15% below that of the branded drug; afterwards, the price was assumed to decrease rapidly to 10% of the branded drug's price. A 9% discount rate was assumed for both pharmaceutical companies and private insurance companies [30].

Sensitivity analyses were conducted regarding launch delay, SoV, duration of patents (for innovators and me-too drugs) and the impact of the first entrant's generics on the sales of me-too drugs. No sensitivity analyses were conducted for discount rate, me-too uptake, generics pricing, market size or average price of the incumbent.

2.8. Societal Perspective

The US health insurance market was assumed to be perfectly competitive and payers' savings were passed entirely on to consumers (otherwise, the zero-profit assumption is violated). The producer surplus is the excess of revenue over total variable costs [31]. When a second entrant decides to launch a me-too drug, the variable costs are related to promotional investment and product; however, the research and development costs are sunk and are not variable.

The economic surplus is the sum of the consumers' and producers' surplus:

$\int_{P_1}^{P_0} D(P)dP + D_1 \cdot P_1 - D_0 \cdot P_0 - \Delta VC$ where D_0, P_0 are the average demand and price before the me-too is launched. D_1, P_1 are the average demand and price after the me-too is launched. ΔVC are the increase in variable costs generated by the launch of the second entrant.

2.9. Impact of Me-too Drugs on Market Growth

A before and after approach was used to assess new entrants' impact on market growth. Two monthly variables were introduced as independent variables: a time trend variable and a second variable that captured the new entrant's impact, which was zero before the new entrant launched and was increased by one unit per month after the new entrant launches. It was not possible to use this approach for all markets because the entry of a third or fourth product confounds the results in most markets. In addition, the time difference between the first and second entrants' launches was sometimes not sufficient to establish robust before and after trends.

3. Results

Overall, 27 products were identified as second entrants with limited differentiation (table I). The 'average' me-too drug was launched 2.5 years (10 quarters) after the first entrant, with a 54% SoV and a 4% WAC discount, and captured 38.5% of market share.

The results of the regression analysis for equations [2] and [3] are presented in tables II and III.

3.1. Peak Market Share

The impact of SoV on the peak market share is highly significant ($p<0.001$). An increase of 1% in (1+SoV) leads, on average, to a peak share increase of 0.758 of a percentage point. The launch delay variable was found to be significant in both the market share model ($p<0.001$) and the price model ($p<0.05$). Each additional delay of one quarter reduced the peak share potential by 1.1 percentage points ($p<0.001$) and the price potential by 0.6 percentage points ($p<0.05$). Second-entrant delay (in quarters) multiplied by 1.1% represents the actual first-mover advantage expressed in market-share points.

The model predicted an average peak share of 38.7% (vs an actual share of 38.5%; table I). A few products achieved a share substantially higher or lower than predicted: Zoloft (actual share +7 percentage points vs predicted), Reyataz (+7 points), Foradil (+6 points), Allegra D (+7 points), Femara (–11 points), Exelon (–9 points), Symbicort (–7 points), Onglyza (–6 points) and Zomig (–6 points).

If a product launched very late (e.g. 15 quarters later than the incumbent) without any promotional investment, one would expect its market share to be minimal and, indeed, the model predicted a peak share of less than 1%.

3.2. Model Validation

Results from the White, Ramsey and Shapiro–Wilk *W* tests (p=0.47, p=0.25 and p=0.33, respectively), the value of the variance inflation factor (1.0), and the lack of relationships between residuals and fitted values (figure 1), indicated that the ordinary least-square finite sample assumptions were not violated.

The results changed slightly when Zestril was assumed to be a me-too of Prinivil, The intercept was 0.15 (p=0.02) and the coefficient of the ln(1+*SoV*) was 0.793(p=0.000) and the coefficient for the launch delay did not change. The impact of removing the points whose leverage value was at least twice as high as the average is shown in table II. In practice, three observations (Prinivil/Zestril, Actos and Starlix) were removed. The significance and the magnitude of the coefficients of delay and SoV are comparable to those in table II. No observations were found to be influential (i.e. Cook's distance > 4/N, where N is the number of observations in the dataset).

3.3. Market Share Model Specification

Table II presents the impact of adding covariates to the core model. Price discount was not found to be a significant variable for market share (p=0.77). SoV in the second year did not have a significant impact on the peak share potential (p=0.42). The time trend coefficient was negative but was only significant if the significance threshold was raised to 10% (p=0.063). Given the low number of observations, a significance level of 10% is acceptable. The sign of the trend variable showed that the first-in-class drug's advantage increased over time. When the interaction variable between launch delay and ln(1+SoV) was introduced, ln(1+SoV) and the interaction coefficients were not individually significant but were jointly significant (Chow test p<0.001). The interaction variable added marginal information to the core model (Akaike's Information Criterion [AIC] of –80.0 vs –78.2).

3.4. Payer's Perspective: Cost-Saving Estimates

Regardless of price discount assumptions, the cumulative savings from me-too drugs were found to be minimal in the first quarters because the second entrant's share was minimal (figure 2a). The cumulative, discounted savings peak occurred before the first entrant became generic, and were over $1000 million if the launch price was 15% below the incumbent's price. After the first entrant becomes generic, the savings decrease because the second entrant becomes more expensive than the generics. Given the aggressive pricing strategies for generics, savings decreased rapidly and only amounted to $450 million over the me-too drug's lifecycle. If the price discount was less than 10%, cumulative savings generated by the second product were negative over the lifetime of the me-too drug.

Assuming a 15% price discount, the savings for payers from products launched with 69% SoV were 18% higher than those generated by products launched with 54% SoV, while the savings from products launched with 39% SoV were 20% lower (figure 2b).

The results of the sensitivity analysis around launch delay are shown in figure 2c. Assuming a higher price discount for late entrants (0.6% for each quarter; table III), late me-too drugs generated higher savings than early me-too drugs in the first few years but had less value over their lifetime.

The price discount necessary for a me-too drug to be cost saving was marginal if the me-too drug was launched a few quarters after the pioneer. However, if the me-too drug was delayed by 5 years, a price discount of 23% CI: 17%-35%) was necessary (figure 3). This is because the me-too drug prevents generic utilization for a long period after the first entrant loses patent. The number of years with patent protection is uncertain and varies across drugs, so a confidence interval for the required price discounts was created based on 20 000 simulations (1000 for each quarter of delay). The results of the simulations show that a price discount of up to 35% may be required for a late me-too drug to be cost saving (figure 3). Managed care

organizations have become more aggressive in managing brands' prescriptions once an innovator loses patent. For instance, Lipitor's market share decreased by an additional 0.01% (0.004 point) per month after Pravachol's generics were introduced (data not shown). When overlaying a similar share decrease for me-toos once the innovator lost patents, the results of the simulations showed that the a price discount of 21% (95% CI: 16%-32%) for a late me-too drug (i.e. delayed by 5 years). Therefore, managed care intervention only slightly increases the value of me-too drugs.

3.5. Impact of Me-too Drugs on Market Growth

The results of the analysis of new entrants' impact on market growth for the erectile dysfunction and the sleeping aid markets are presented in table IV and figure 4. In both markets, the before and after trend variables were highly significant. The erectile dysfunction market grew at a rate of 11 000 TRx per month and the sleeping aid market at 20 600 TRx per month before new entrants entered the market. However, the markets had opposite growth patterns after the new launches. The market growth increased by 30 500 TRx per month for the sleeping aid market but decreased by 7500 TRx per month in the erectile dysfunction market. One potential explanation for the decrease in TRx for erectile dysfunction drugs was a scare linking them to blindness in 2005 [32]. If the analysis was halted at the end of 2004, the trend after second entrant launch coefficient was positive but insignificant.

3.6. Societal Perspective

Using the assumptions described in Section 2.7. and assuming that the me-too launch price is 15% below the incumbent's price, the cumulative increase in consumer surplus is approximately $525 million regardless of the market growth (i.e. for sleep or erectile dysfunction markets). The change in producers' surplus depends on market growth

assumptions. If the market does not grow, the producers' surplus decreases by $525 million plus any additional variable costs. The economic surplus always decreases since no incumbent decreased promotional investments when competition entered the market. If the market grows at the same rate as the sleep market (approximately 20% incremental growth after 24 months), the producers' surplus grows by $3500 million minus any increase in variable costs. The launch of a me-too drug increases the economic surplus only if the increase in variable costs does not exceed $4075 million over the life of the me-too drug (i.e. approximately $300 million per year). This was not the case for the sleep market since SDI health reported that the promotional investments increased by $700 million a year after the introduction of me-toos.

4. Discussion

4.1. Pharmaceutical companies' perspective

The model has enabled an objective analysis of several of the factors influencing the success of me-too drugs. A number of observations can be made based on the model's output.
Some products performed much better (or worse) in reality than predicted by the model. There could be a number of explanations for this, for example the ability to differentiate or the competition's focus.
With regard to the delay between launch of the first entrant and the me-too drug, the longer a second entrant is delayed, the less share it is likely to capture and the lower its price. The first entrant is therefore better established, and the ability of a me-too drug to gain market share is reduced and payers are more likely to demand a lower price to reimburse the product.
It is possible for pharmaceutical companies to offset launch delays with an increased SoV to achieve a target market share. The required increase in SoV can be calculated by

differentiating equation [2] assuming the peak share target remains constant. The formula to offset a delay is:

$$d\mathit{SoV}/(1 + \mathit{SoV}) = (-\gamma/\beta) * d\mathit{T} \quad \textbf{[4]}$$

By using the regression coefficients in table II,

$$d\mathit{SoV}/(1 + \mathit{SoV}) = -1.48\% * d\mathit{T} \quad \textbf{[5]}$$

For instance, a company planning to launch a me-too drug with a 50% SoV and facing a one-quarter delay has to increase its SoV to 52.2% to reach the same peak share that would have been achieved without the delay. Therefore, the company will have to increase the planned promotional investment by 9.2%. Approval delays can therefore be very costly for companies.

It is worth noting that the constant in the price model is not significant: if the first entrant and the second entrant launch within the same quarter, prices are expected to be equivalent, which makes intuitive sense (table III).

The implications of the results presented in tables II and III are fundamental for the pharmaceutical industry, if the results are generalized beyond the analysed time-frame (more on this in Section 4.2.3.). To gain market share, pharmaceutical companies should focus on promotional investments. Investing at the appropriate level over the first 12 months after launch greatly influenced the success of the drug. More specifically, the model can help pharmaceutical companies to determine the promotional investment that maximises profits and to understand whether investing in research for a me-too drug is commercially sound. As the adjusted R^2 in the peak share model is 0.74, other factors account for at most 26% of the success. The level of promotional investment, rather than its quality, seems to matter most. This point is further discussed in Section 4.6.

4.2. Market Share Model Specification

4.2.1. Price Discount Impact

Price discount was found not to be a significant variable for market share. In other words, it cannot be shown that increasing the price discount at launch helps a product to increase its market share potential. A feasible explanation is that physicians and patients are not usually exposed to the actual price of the drugs. In general, physicians do not pay for the drugs and patients' co-payments are typically not linked to drug prices (with the exception of co-insurance). Also, price cannot be considered as a competitive advantage as the price of the first entrant can easily be lowered to match that of the second entrant. The implication of this finding is that aggressive pricing is not recommended as it does not significantly impact share. However, managed care organisations seem to have become more aggressive in managing prices recently, and the impact of pricing decisions may increase in the future.

4.2.2. Share of Voice: First Year Versus Second Year Impact

Although the model predicted that a company's promotional investment level in the second year does not have a significant impact on the peak share potential, it should be noted that one cannot conclude that companies should only invest for 12 months and then stop promotion as no companies have experimented with such a promotional investment pattern.

4.2.3. Time Trend

The time trend coefficient was negative, meaning that the first in class's advantage increased over time. In other words, and with everything else being equal, it was better on average for a me-too drug to launch in the 1990s than in the 2000s. One potential explanation is the increasing impact of managed care organisations influencing sales. Over time, managed care organisations have become more and more effective in managing formularies and influencing

physician's prescribing patterns. For instance, Express Scripts, one of the largest pharmacy benefit management companies in the USA, erased Lipitor from its list of preferred drugs in 2005 [33]. The intent was clearly to entice patients to use a competitor, Zocor (simvastatin), which was soon to become generic. It should be noted that the time trend coefficient is not significant. This may be due to the low number of products recently launched in the sample.

4.3. Payer's Perspective

The median list price discount observed in the model (4%) is not sufficient for a me-too drug to be cost saving. Additional rebates beyond the list price discount are necessary to ensure that savings are generated over the lifetime of the product.

As savings depend on SoV, price discount and launch delay, payers should consider these three variables when evaluating me-too drugs. For instance, they could calculate the rebates necessary to ensure that a new entrant will be cost saving over its lifecycle.

A late me-too drug represents an expensive alternative to the incumbent's generic over a longer timeframe. In particular, the cumulative savings are negative for me-too drugs launched 5 years after the first entrant, even if sold at a price 21% below that of the first entrant, unless managed care organisations are able to drive generic utilisation in the market.

4.4. Impact on Market Growth

Market growth could represent a cost or a saving for payers. While incremental market growth generates additional drug costs, it could also represent a benefit if incremental usage is directed towards appropriate patients. The introduction of new sleeping aids considerably increased the size of the market but it is unclear whether this increase was driven by an increase in diagnoses of sleeping disorders or "disease mongering". The impact of DTC promotion can be seen as an insightful analogue. Some studies show that DTC advertising

can increase compliance and the likelihood that patients receive the appropriate treatment [34,35]. However, it might also increase overuse and off-label use [34].

4.5. Impact of using the FDA instead of the HAS ratings

Out of the 27 products in the sample, all but three went through the FDA's standard review process. The priority review status of Vioxx and Actos is not incompatible with a me-too classification since their approvals were within one month of Celebrex and Avandia. Kaletra would be excluded from the sample if the FDA classification was used.

All second entrants approved by the FDA from 1999 to 2007 were screened and classified as potential me-too drugs if they went through a standard review process were dispensed at a pharmacy and sales were reported. Inspra and Pylera were the only potential me-toos that were not included in the sample since Inspra received an ASMR of III (vs. Aldactone) and Pylera was not reviewed by the HAS. Therefore, using the HAS or FDA classifications did not dramatically alter the sample.

4.6. Limitations

Several caveats and shortcomings should be considered with regard to some of the data used in this study. Firstly, although ex-factory prices are publicly available, any rebates offered by manufacturers to secure reimbursement are not disclosed; therefore, the actual prices paid by payers cannot always be accurately assessed. In an effort to create a perception of differentiation, pharmaceutical companies try to differentiate me-too drugs from existing options by targeting different patient segments or different points in the therapy algorithm, or by conducting DTC advertising.

The IMS and SDI Health data are based on sampling. A small sample size can make the estimate unstable, and caution should be used when interpreting SoV because the corresponding confidence intervals could be large.

As discussed above, me-too drugs may provide additional benefits to some patients and, therefore, may bring more than cost savings. However, the quantification of those benefits is not readily available and could not be incorporated in the model.

The model could suffer from the following biases: (1) Bias due to measurement. Survey data are prone to measurement error and the level of promotional investments may not be accurately recorded which would bias the regression coefficients downward. The model estimated share as a function of a constant, promotional investment, time delay and an error term ε. Quality of the promotional investment is not reported and, if quality impacts share, it is part of the error term ε. It is plausible that physicians might over-report the quantity of promotional investment for products with effective promotional campaigns. In other words, the quality (unmeasured) and the quantity (measured) of the promotional investment might be correlated. In that case, the error term ε and the independent variable (promotional investment) would be correlated. This would be a violation of the OLS assumptions and the regression coefficients would be biased. A possible solution to these issues is to gather data directly from pharmaceutical companies. (2) Causality bias. It was assumed that SoV drives market share but it is also plausible that manufacturers' expectations of market share drive launch promotional investment decisions. However, we do not believe that causality is an issue as it is unlikely that manufacturers can identify products with high potential share a priori, given the limited differentiation of me-too drugs.

The analysis was conducted for products sold in the retail channel. For products sold by specialty pharmacies or hospitals, the results may differ from those presented in this paper.

5. Conclusions

Me-too drugs have a substantial market impact and can represent considerable sales potential for pharmaceutical companies. On average, they launch with 20% more resources than the

incumbents and they capture 38% of market share within 4 years. The model allowed an objective analysis of some of the factors that impact on the success or otherwise of me-too drugs. The peak market share depends on the promotional investment at launch and the length of the innovator drug's launch advantage. Me-too drugs are introduced at a reduced price compared to incumbent products. The magnitude of the discount depends on the delay between the launch of the incumbent and the me-too drug; however, the price discount does not have a significant impact on market share. In other words, manufacturers' pricing decisions within the customary range do not impact on the potential market share.

In certain circumstances, me-too drugs are cost saving for payers. Namely, price discounts have to be sufficient and me-too drugs have to be launched within a few years after the first entrant. If me-too drugs are launched late, they could save payers money in the short and medium term, but could represent a cost in the long term, as they prevent conversion to low-priced alternatives after the first entrant becomes generic. Managed care organisations can increase the overall value of me-too drugs by providing incentives to switch from me-too drugs to generic versions of the first entrants. The tactics used by some managed care organizations to convert Lipitor utilization to generic simvastatin can be used to increase the value of me-toos [33]. In all scenarios analysed, cost savings are small in the first 2 years of the me-too product's lifecycle. Therefore, if managed care organisations have a short-term financial focus, me-too drugs do not offer financial benefits and only provide additional treatment choices to physicians and patients.

To further assess the value of me-too drugs, a similar analysis could be conducted for hospital products and for products launched as third or fourth entrants into the market. A cross-sectional time-series analysis of R&D investment decision could shed more light on the impact that me-too drugs have on innovation.

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Figure

Fig1. Residuals versus predicted market shares

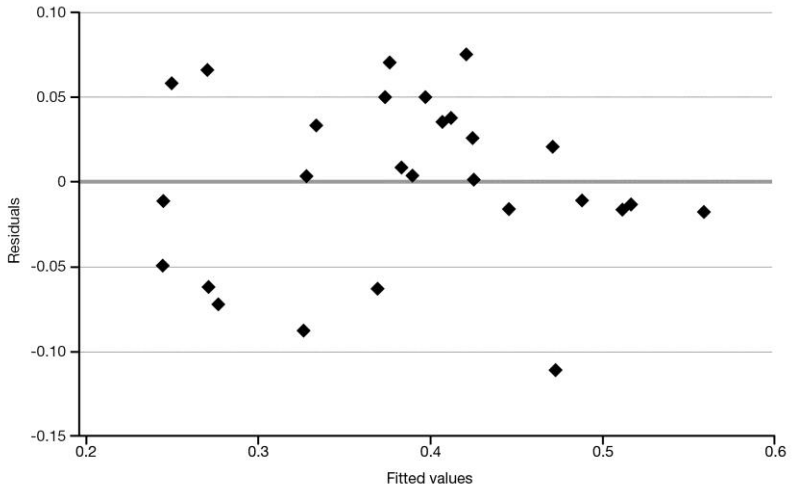

Fig 2. Impact on payers' cumulative savings of (a) price discount, (b) launch share of voice, and (c) launch date.

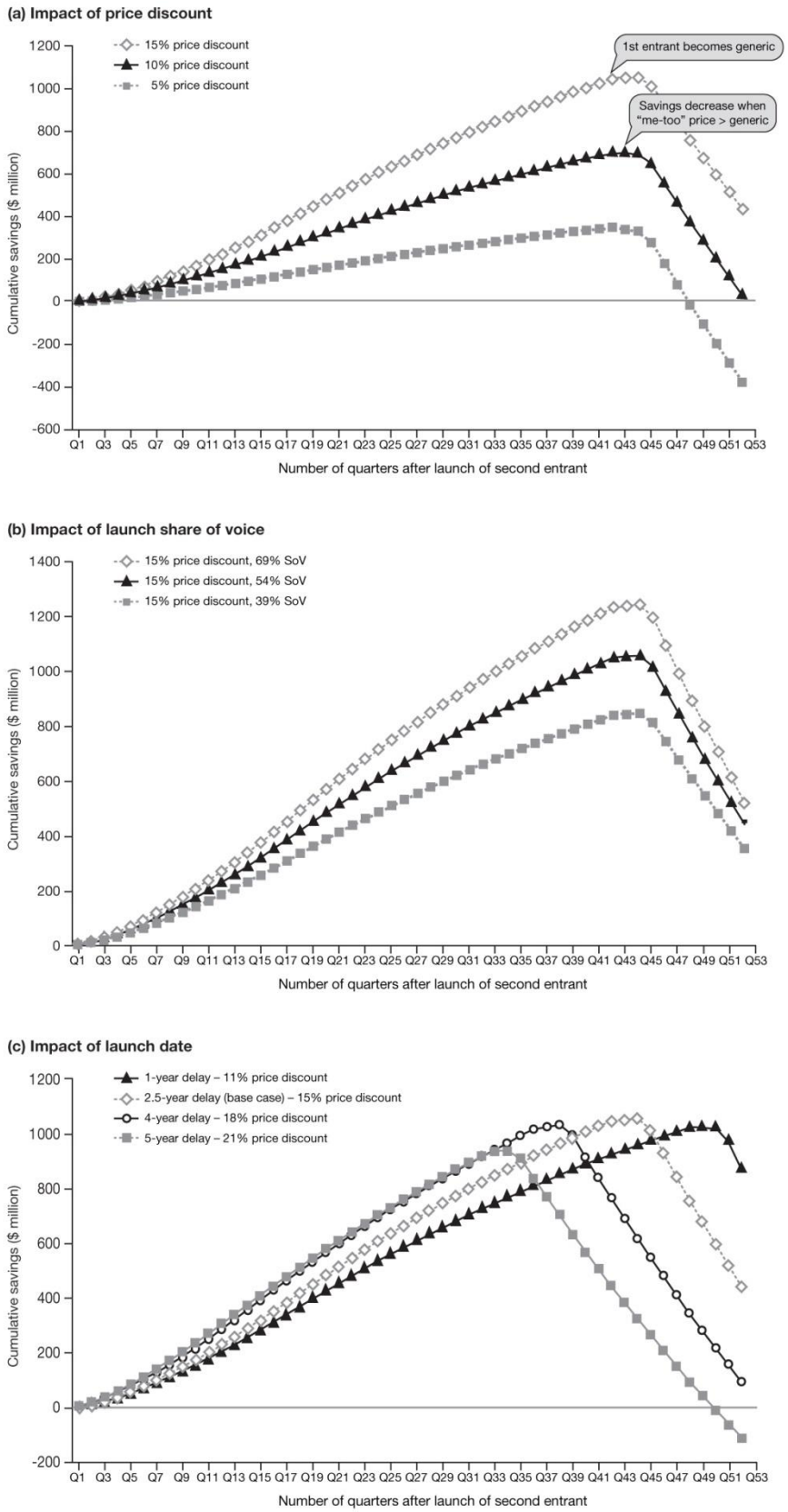

Fig 3. Price discount required for a me-too drug to be cost saving.

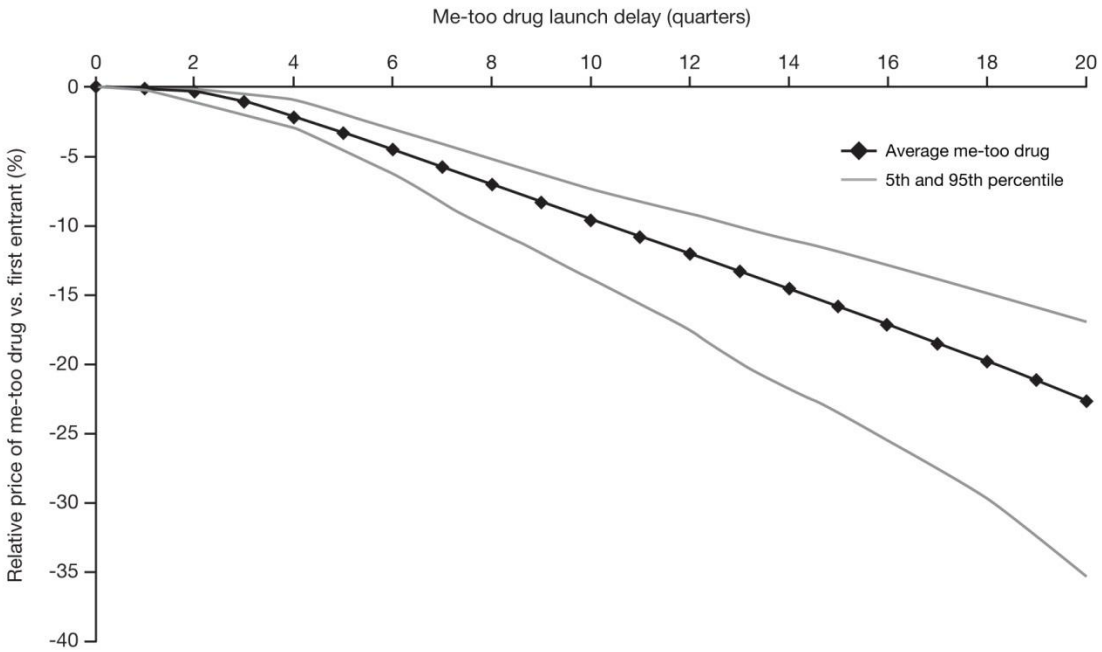

Fig 4. Before-and-after analysis: impact of new entrants in (a) erectile dysfunction and (b) sleeping aid markets.

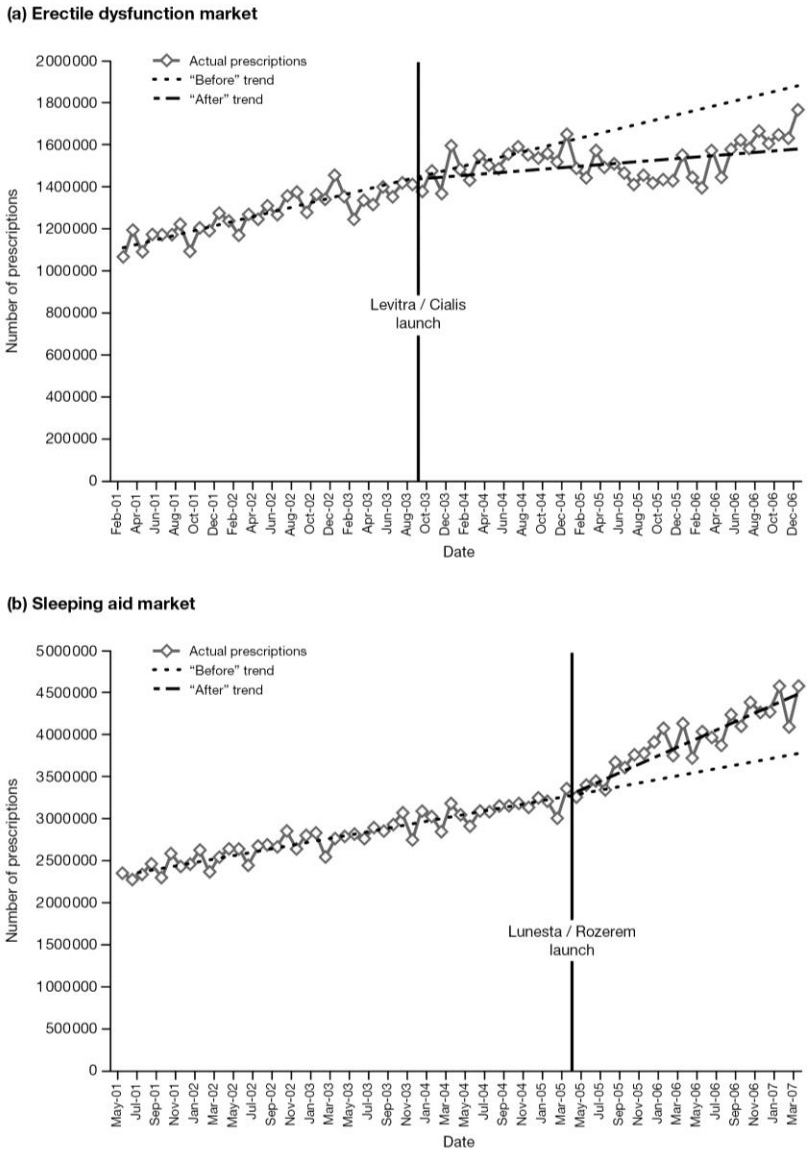

Table I. 'Me-too' drugs selected for analysis

1st entrant	2nd entrant	ASMR rating[a]	US launch	Launch delay (quarter)	Relative WAC at launch (%)	Peak share (%)	Launch SoV (%)
Celebrex	Vioxx	Same as Celebrex	May 1999	1	0	49	51
Imitrex	Zomig	None vs Imitrex	Dec 1997	15	–12	21	42
Claritin	Zyrtec	None vs Claritin	Jan 1996	11	–9	39	55
Cozaar	Diovan	V	Feb 1997	7	–3	48	68
Fosamax	Actonel	None vs Fosamax	Apr 2000	15	–10	33	53
Mevacor	Pravachol	Not available[b]	Nov 1991	15	–9	39	66
Prilosec	Prevacid	None vs Prilosec	May 1995	15	–8	37	54
Serevent	Foradil	None vs Serevent	May 2001	15	–8	31	38
Prozac	Zoloft	None vs Prozac	Feb 1992	15	–2	45	63
Aricept	Exelon	IV (same as Aricept)	May 2000	13	4	24	49

Avandia	Actos	V (same as Avandia)	Jul 1999	0	16	45	40
Zestril	Prinivil	Same molecule	Jan 1988	0	0	45	37
Risperdal	Zyprexa	IV vs Risperdal	Oct 1996	11	–6	45	58
Flonase	Nasonex	IV (same as Flonase)	Oct 1997	11	–2	42	54
Claritin D	Allegra-D	Same as Claritin D	Jan 1998	13	–18	34	37
Claritin	Zyrtec + Allegra	Same as Claritin	Jan 1996	11	–9	43	64
Viagra	Cialis + Levitra	V vs Viagra	Aug 2003	15	–5	44	70
Humalog	Novolog	V vs Humalog	Sep 2001	15	–8	23	37
Exforge	Azor	Same as Exforge	Oct 2007	1	–2	43	46
Concerta	M-CD + Add-XR	Similar molecule[c]	May 2001	3	0	54	74
Advair	Symbicort	IV (same as Advair)	Jun 2007	15	–11	20	43
Januvia	Onglyza	V (same as Januvia)	Aug 2009	11	0	31	53

Lantus	Levemir	Same as Lantus	Mar 2006	15	2	19	37
Sprycel	Tasigna	Same as Sprycel	Nov 2007	5	–16	50	69
Kaletra	Reyataz	Same as Kaletra	Jun 2003	11	23	49	63
Arimidex	Femara	Same as Arimidex	Jul 1997	6	0	36	63
Prandin	Starlix	Same as Prandin	Feb 2001	11	–6	50	86
	Average			**10**	**–4**	**38**	**54**
	Median			**11**	**–5**	**42**	**54**
	Minimum			**0**	**–18**	**19**	**37**
	Maximum			**15**	**+18**	**54**	**86**
	No. of observations			**27**	**27**	**27**	**27**

Sources: French HAS [22], IMS [23], SDI Health [24], First Databank [25].

ASMR = Amélioration du Service Médical Rendu (evaluation of therapeutic benefit); **M-CD + Add-XR** = Metadate CD + Adderall-XR; **SoV** = share of voice; **WAC** = wholesaler acquisition cost.

[a] Same: the French HAS determined that the second entrant shares the same improvement benefits as the first entrant; None: HAS determined that the second entrant does not bring any additional benefits compared with the first entrant.

[b] Pravachol was not evaluated against the first entrant (Mevacor) by HAS, since Mevacor was not launched in France. The author's judgement of ASMR rating was used.

[c] Metadate CD and Concerta are both methylphenidate hydrochloride with extended **release** formulation. Concerta and Adderall XR have similar efficacy and side effects.

Table II. Coefficient estimates: second-entrant peak share model results

	Basic model	**Basic model without leverage**	**With price discount**	**With 2nd year SoV**	**With interaction**	**With time trend**
Constant (%)	17.3**	9.7	17.2**	15.5*	34.5**	21.8***
Delay vs 1st entrant (%)	–1.1***	–0.9**	–1.1***	–1.2***	–2.8**	–1.1***
ln(1 + SoV) (%)	75.8***	87.6***	75.8***	68.7***	32.6	75.0***
$\ln(1 + SoV_{2ndyear})$ (%)				12.8		
Price discount (%)			4.1			
Delay*ln(1 + SoV) (%)					4.3	
Time trend (years) (%)						–0.4
Adjusted R^2	0.74	0.73	0.73	0.74	0.76	0.77
Observations	27	24	27	27	27	27

*p<0.05; **p<0.01; ***p<0.001. **SoV** = share of voice.

Table III. Coefficient estimates: second-entrant price model results

	Coefficient (%)	**Standard error**	**p-value**
Constant	2.5	0.033	0.451
Delay vs 1st entrant	–0.6*	0.003	0.041

R^2=16%; adjusted R^2=12%.

*p<0.05.

Table IV. Impact of new entrants on market growth (before and after analysis)

	Sleeping aid[a]	**Erectile dysfunction**[b]	**Erectile dysfunction (until Dec 2004)**
TRx constant (×1000)	2335.6***	1114.5***	1126.4***
Trend before 2nd entrant launch (TRx/month)	20.6***	11.0***	9.8***
Trend after 2nd entrant launch (TRx/month)	30.5***	–7.5***	1.6

***p<0.001.

[a] Prais-Winsten regression was used to correct for the errors' serial correlation ["prais" procedure was used in Stata].

[b] A regression with robust estimator of variances was used to correct for heteroscedasticity ["vce(robust)" option was used in Stata].

TRx = number of prescriptions.

Drug versus vaccine investment: a modelled comparison of economic incentives.

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Abstract

Background: Investment by manufacturers in research and development of vaccines is relatively low compared with that of pharmaceuticals. If current evaluation technologies favour drugs over vaccines, then the vaccines market becomes relatively less attractive to manufacturers.

Methods: We developed a mathematical model simulating the decision-making process of regulators and payers, in order to understand manufacturers' economic incentives to invest in vaccines rather than curative treatments. We analysed the objectives and strategies of manufacturers and payers when considering investment in technologies to combat a disease that affects children, and the interactions between them.

Results: The model confirmed that, for rare diseases, the economically justifiable prices of vaccines could be substantially lower than drug prices, and that, for diseases spread across multiple cohorts, the revenues derived from vaccinating one cohort per year (routine vaccination) could be substantially lower than those generated by treating sick individuals.

Conclusions: Manufacturers may see higher incentives to invest in curative treatments rather than in routine vaccines. To encourage investment in vaccines, health authorities could potentially revise their incentive schemes by: (1) committing to vaccinate all susceptible cohorts in the first year (catch-up campaign); (2) choosing a long-term horizon for health technology evaluation; (3) committing higher budgets for vaccines than for treatments; and (4) taking into account all intangible values derived from vaccines.

Keywords

Incentives, Vaccines, Drugs, Research and Development, Investment, Net present value

Background

It has been argued that the vaccines market is not attractive to manufacturers [1]. Even with the successful launches of vaccines against pneumococcal and human papilloma virus diseases and pandemic influenza, vaccines' share of the global medicines market remains marginal at approximately 3% (2010 figures) [2,3]. Historically, manufacturers have preferred to invest in potential blockbusters and the number of manufacturers producing vaccines in the USA dropped from 37 to 10 between 1967 and 2002 [1,4,5]. Currently, four-fifths of the market is held by only five manufacturers [3]. As a consequence, investment in vaccines is relatively low, with manufacturers only spending $750 million on research and development (R&D) for vaccines in 2000 compared with $26.4 billion for pharmaceuticals [1,6]. One of the factors explaining the situation is low pricing, driven by the fact that not all of the intangible value may be taken into account when vaccines are evaluated [5-8].

We therefore developed a mathematical model to elucidate whether the methodologies currently used to evaluate new technologies favour drugs over vaccines. We modelled the decision-making process of manufacturers when deciding to invest in a vaccine or a drug to combat a disease that affects children, by analysing the interactions between manufacturers and payers. In this article, we report the model and also discuss the reasoning behind and potential implications of each finding. Since the major vaccines manufacturers (GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi) also produce treatments, the question is particularly relevant and important. It should be highlighted that (i) the model intends to assess the *relative* attractiveness of vaccines compared to drugs and does not intend to evaluate the *absolute* attractiveness of the vaccines market, and that (ii) the article only explores the economic arguments (scientific arguments are only evoked where relevant). Please note that economic arguments are not the only elements under consideration when a

decision is made. For instance, a risk-free inactivated polio vaccine would not be recommended if cost-effectiveness was the only decision criterion [7].

Methods

The model

The model describes investment in technologies to combat a disease that affects children from the perspectives of the manufacturer and the regulator or payer. The disease impacts n_c cohorts of children (i.e., from age 0 to $n_c - 1$) (Table 1 provides a summary of terms used in the model). The larger n_c is, the more widespread the disease. Each cohort size is normalized to 1 (or 100%). The probability of becoming sick is uniformly distributed across cohorts and is equal to s per year in each cohort.

The model consists of two players: the manufacturer who decides to invest in the technology and the regulator/payer who sets the price and the demand by determining the individuals eligible for treatment. The timing of the game is as follows: first, the regulator announces how new health technologies are to be evaluated and used; the manufacturer then decides to invest in a treatment (drug) or in prevention (vaccine). The regulator can decide to use the potential vaccine to either (i) vaccinate infants in their first year of life (routine vaccination); or (ii) vaccinate infants in their first year of life and vaccinate all susceptible cohorts (routine vaccination plus catch-up). The efficacy of the drug and the vaccine are assumed to be the same. If all sick individuals are treated (or all susceptible cohorts are vaccinated), the current disease costs are assumed to be eliminated. There is no asymmetry of information between the regulator and the manufacturer.

We will now describe each player, and their objective and strategy.

The regulator

The regulator can set the price of new technologies based on two potential criteria: (i) budget impact; or (ii) cost-effectiveness. It should be noted that, among other criteria, the French authorities usually apply budget impact-related arguments when negotiating the price of new

technology with manufacturers, while the National Institute for Health and Clinical Excellence for drugs in England and Wales and Joint Committee on Vaccination and Immunisation for vaccines in the United Kingdom use a cost-effectiveness framework [9].

In the budget-impact framework, the regulator is willing to accept a new technology provided that incremental costs are below a certain annual budget threshold B_j, where $j = 0$ for treatment and $j = 1$ for prevention. In the model, the allocated budget could be different for treatment and prevention. Therefore, the new technology is accepted if:

$$\sum_{i=1}^{t} \frac{Q_{ji}P_{ji} - CA_{ji} - B_j}{(1+r_r)^i} \leq 0 \qquad \textbf{(1)}$$

where Q_{ji}, P_{ji}, and CA_{ji}, are the quantity, price paid, and cost avoided in year i for product j; r_r is the discount rate used by the regulator; and t is the time (in years) used in the economic evaluation of the new technologies by the regulator (i.e., the time horizon) (see Table 1).

In the cost-effectiveness framework, the ratio of incremental costs and humanistic benefits is evaluated and compared with a threshold λ. The new technology is accepted if:

$$\frac{\sum_{i=1}^{t} \frac{Q_{ji}P_{ji} - CA_{ji}}{(1+r_r)^i}}{\sum_{i=1}^{t} \frac{E_{ji}}{(1+r_r)^i}} \leq \lambda \qquad \textbf{(2)}$$

where E_{ji} is incremental quality-adjusted life-years gained in year i for product j.

In the rest of the article, we will only use the budget-impact framework as equation **(2)** can be considered to be a particular case of equation **(1)** with:

$$B_j = \frac{\lambda \cdot \sum_{i=1}^{t} \frac{E_{ji}}{(1+r_r)^i}}{\sum_{i=1}^{t} \frac{1}{(1+r_r)^i}}$$

The manufacturer

The manufacturer chooses to develop the vaccine rather than the drug if the expected profits of the vaccine exceed those of the drug **(3a)** and are positive **(3b)**:

$$E[\sum_{i=1}^{l+d} \frac{(S_{1i}M_{1i} - C_{1i}) - (S_{0i}M_{0i} - C_{0i})}{(1+r_m)^i}] \geq 0 \quad \textbf{(3a)}$$

and

$$E[\sum_{i=1}^{l+d} \frac{S_{1i}M_{1i} - C_{1i}}{(1+r_m)^i}] \geq 0 \quad \textbf{(3b)}$$

where S_{ji} are the sales, M_{ji} the gross margins, and C_{ji} the cost associated with developing, marketing and selling the health technology j in year i; r_m is the discount rate used by the manufacturer; d is the number of years after launch used for the economic evaluation; l is the number of years required to develop the technology before launch; and $l+d$ is the total number of years under consideration in the economic evaluation by the manufacturer. The condition **(3b)** ensures that the net present value of the vaccine's profits is positive.

Assumptions and definitions

There are a number of simplifying assumptions in the model: (i) The regulator sets a unique price during the game (i.e., $P_{ji} = P_j$). (ii) Once a regulator defines the individuals eligible to receive the new health technology, all eligible individuals receive it and are reimbursed by the payer. In other words, the adoption is immediate and the coverage rate is 100%. (iii) The regulator and the manufacturer use the same time horizon to make a decision after the new product's launch (i.e., $d = t$). (iv) The gross margins, costs of development, marketing costs, patent protections, and probabilities of success are assumed to be identical between the technologies (i.e., $C_{1i} = C_{0i}$). In particular, this implies that a vaccine is not more or less scientifically difficult to develop than a curative treatment. This assumption allows specific focus on the impact of the evaluation framework and not on the products' characteristics. The

impact of this assumption is discussed later in this article. (v) The annual cost of the disease (c_C) is constant for each cohort. (vi) The number of years considered for evaluation exceeds the number of cohorts (i.e., $t \geq n_c$).

Definition for discounting factor in the t^{th} year:

$$y_t(r) = \frac{1}{(1+r)^t} \quad \textbf{(4)}$$

Based on Assumptions iii and iv, the manufacturer chooses the technology with the higher discounted revenues after launch, and condition **(3)** can thus be rewritten as:

$$\sum_{i=1}^{t} \frac{S_{1i} - S_{0i}}{(1+r_m)^i} \geq 0 \quad \textbf{(5)}$$

Results and discussion

The maximal justifiable prices accepted by the regulator and, therefore, the maximal revenues generated by the manufacturer, are summarised in Table 2. All proofs can be found in Additional file 1.

Price

Unlike the price of treatment, the price of a vaccine is independent of *s*, the annual percentage of children in susceptible cohorts falling ill. This is because the number of individuals receiving a vaccine is independent of *s*, and only the overall cost of the disease (and not the cost per sick individual) matters when the price is evaluated.

The price of the treatment is independent of the treatment horizon used for the evaluation because the benefits and costs are the same for each year. As $1+n_c r_r \geq 1+r_r$ and $\psi_{t-1}(r)$ decreases with *t*, the price of the routine plus catch-up vaccine increases with *t*, i.e., the longer the time horizon chosen by the regulator, the higher the justifiable price. Similarly, the economically justifiable price of the routine programme increases with *t*. The price of the routine plus catch-up vaccine and the price of routine vaccine decrease with the regulator discount rate, r_r.

Assuming $B_0 = B_1$ (i.e., the payer is indifferent about investing in preventive versus curative technologies), the ratio between the justifiable price of a vaccine used for a routine and catch-up programme and the price of the treatment is:

$$P_1 / P_0 = sn_c \frac{1+r_r-\psi_{t-1}(r_r)}{1+n_c r_r-\psi_{t-1}(r_r)} \leq sn_c$$

Consistent with the findings of Baumann [8], we find that a vaccine's economically justifiable price can be considerably lower than that of a treatment for diseases with low

prevalence across cohorts (i.e., those with a small sn_c). However, this is not generally true for more widely prevalent diseases.

Revenues

The treatment generates annual sales of ($c_c n_c + B_0$), which is the sum of the cost savings generated by the drug and of the incremental budget the regulator is willing to pay to eradicate the disease.

The revenues are a function of the total cost of the disease $c_c n_c$ and are independent of s for the treatment and the vaccine. Therefore, if the economics of equation **(5)** are followed, the decision to invest in a vaccine rather than a drug does not depend on the prevalence of the disease, but on the total cost of the disease. However, if we relax the assumptions of constant margins and costs, this conclusion may no longer be valid (see Section 3.4).

If there is only one sick cohort (i.e., $n_c = 1$), the revenues are the same for all scenarios.

Routine plus catch-up versus treatment

The ratio between the revenues generated by the routine plus catch-up vaccination and those generated by the treatment is:

$$\left[\frac{1-\psi_t(r_r)}{1-\psi_t(r_m)} \cdot \frac{1+r_r}{1+r_m} \cdot \frac{1+n_c r_m - \psi_{t-1}(r_m)}{1+n_c r_r - \psi_{t-1}(r_r)}\right] \cdot \frac{c_c n_c + B_1}{c_c n_c + B_0} = \left[\frac{1+r_r - \psi_{t-1}(r_r)}{1+n_c r_r - \psi_{t-1}(r_r)} \cdot \frac{1+n_c r_m - \psi_{t-1}(r_m)}{1+r_m - \psi_{t-1}(r_m)}\right] \cdot \frac{c_c n_c + B_1}{c_c n_c + B_0}$$

The ratio decreases with r_r and increases with r_m, and is composed of two parts: (i) ratios of functions of the manufacturer and regulator discount rates; and (ii) the ratio of disease costs and budgets. It is worth noting that the revenues are identical if the regulator is indifferent about treatment versus prevention (i.e., $B_1 = B_0$) and if the manufacturer and regulator use the same discount rate (i.e., $r_r = r_m$). If $B_1 > B_0$ and $r_m > r_r$, the revenues from routine plus catch-up vaccination are higher than those from the treatment. This is because the relative value of the sales in the first year versus total sales is more important for the manufacturer than for the

regulator if the manufacturer applies a higher discount rate. If *t* becomes large, the ratio approaches:

$$\frac{1+r_r}{1+r_m} \times \frac{1+n_c r_m}{1+n_c r_r} \times \frac{c_c n_c + B_1}{c_c n_c + B_0}$$

The ratio between the first-year revenues for routine plus catch-up vaccination versus those for treatment is:

$$\frac{1+r_r - y_{t-1}(r_r)}{1+n_c r_r - y_{t-1}(r_r)} \times \frac{c_c n_c + B_1}{c_c n_c + B_0} \times n_c$$

If $B_1 = B_0$, this leads to an asymptotic value in *t* of $n_c \frac{1+r_r}{1+n_c r_r}$; in this case, the upfront investment for routine plus catch-up vaccination can be large compared with that for the treatment and may be a barrier to implementation for the payer. If the number of impacted cohorts (n_c) is small, the ratio is only slightly sensitive to the discount rate used by the regulator (r_r). If the disease impacts a large number of cohorts, a small decrease in discount rate increases substantially the first year cost of the catch-up, relative to treatment.

Routine vaccine (without catch-up) versus treatment

As discussed, the price of the routine vaccination increases when *t* increases. However, even if *t* is large, the revenues from routine vaccination are lower than those from treatment. If the new technologies have to be cost neutral (i.e., $B_0 = B_1 = 0$), the discounted sales from routine vaccination are asymptotically $\frac{(n_c - 1)}{2} \times r_r$ times lower than for treatment (as per Proposition 6 in Additional file 1). In other words, if *t* is large, routine vaccination becomes relatively less attractive than treatment as the number of cohorts n_c and the regulator discount rate r_r increase. This result was expected: the relative value of routine vaccination decreases as the number of cohorts increases because it takes many years to eradicate the disease. The

regulator could largely eliminate this bias against routine vaccination by choosing a discount rate close to 0.

It is worth noting that if the technologies are expected to be cost neutral (i.e. if $B_0 = B_1 = 0$), the relative value of each scenario's revenue is independent of c_c. In other words, the annual cost of the disease per cohort is just a normalizing factor in this case.

Numerical illustration

In order to quantify and illustrate the incentives described in Section 3.2, a base case was constructed as follows: the disease impacts 10 cohorts (i.e., $n_c = 10$), and the annual probability of becoming sick $s = 1\%$. The regulator is not willing to spend additional budget on either the vaccine or the treatment ($B_0 = B_1 = 0$), i.e., new technologies have to be cost neutral. A discount rate r_r of 3% was used for the regulator, as recommended by the World Health Organization [10]. A discount rate r_m of 8% was used for the manufacturer [11]. The time horizon used for evaluation was 20 years (i.e., $t = 20$). Similar to the previous model, each cohort size is normalized to 1 (or 100%). The disease cost per cohort c_c was assumed to be \$100.

Based on our model and the assumptions above, the maximal price of the treatment is \$10,000 per individual, while the price of routine vaccination is \$728 and the price of routine plus catch-up vaccination is \$630 (only 6% of the treatment price). The discounted sales over 20 years of the treatment amount to \$9818, those of the routine and catch-up vaccination are \$11,435 and those of routine vaccination only are \$7148 (i.e., 27% below those of the treatment). Therefore, the vaccine price in our numerical example is considerably below that of a drug, and the revenues from a routine vaccination are lower than from the treatment. However, if the regulator decides to implement a catch-up campaign, the revenues from the vaccine become more attractive to the manufacturer than those from the treatment.

The revenues in the first year are $1000 for the treatment, and $6300 for the routine and catch-up vaccination, compared with $728 for the routine vaccination alone. Therefore, the first-year budget impact of a routine and catch-up programme can be seen as prohibitive if the payer has not properly projected the budget needed for introducing the new vaccine.

Sensitivity analysis

Univariate sensitivity analyses around the base case were conducted to assess the impact of key assumptions on the decision-making process. In particular, we modified the number of cohorts impacted by the disease (n_c) while keeping all other assumptions fixed (including the cost per cohort) (see Fig. 1). We concluded that the more widespread the disease, the less favourable the revenue associated with routine vaccination compared to curative alternatives. For instance, if the disease affects 20 cohorts, the sales potential of the routine vaccination is only half that of the treatment. Conversely, the larger the number of affected cohorts, the more favourable is the approach of a vaccination with catch-up, as the revenue in the first year will be very large. By increasing the time horizon, the disadvantage of the routine programme decreases. If t = 100, the difference in revenues decreases to 13% (versus 27% in the base case), which is close to the asymptotic value of $\frac{(n_c - 1)}{2} \times r_r = 14\%$ discussed in Section 3.2.2 (see Fig. 2).

Impact of key assumptions

The validity of some key assumptions and the impact of relaxing them should be considered.

Gross margins

In the above model, it was assumed that gross margins were the same for all technologies. In other words, $\frac{(P_j - c_j)}{P_j}$ (where c_j is the average cost of producing a unit of j over the

evaluation period) is the same for $j = 0$ and $j = 1$. A number of considerations should be taken into account when assessing the validity of this assumption. Margins for vaccines could be lower than those for drugs: (i) because vaccine production is a more complicated (and potentially more costly) process than drug production because vaccines are produced from living organisms that must be grown in a highly controlled environment [1], and (ii) because prices of vaccines are lower than those of drugs (Section 3.1). Conversely, the large economies of scale (because vaccination affects entire cohorts and treatment affects only the percentage *s* of cohorts) could increase margins for vaccines. Therefore, it is possible – but not likely – that margins for drugs and vaccines are identical. If this is not the case, the manufacturer's decision criteria will not be based on comparing discounted revenues as per equation **(5)**, but on discounted revenues minus the cost of goods, which are:

$$\frac{1-\psi_t(r_m)}{r_m} \cdot s \cdot c_0 \cdot n_c \qquad \textbf{(6)}$$

for the treatment, and:

$$\frac{1-\psi_t(r_m)}{r_m} \cdot c_1 \qquad \textbf{(7)}$$

for the routine vaccination. Therefore if $c_1 > c_0 \cdot s \cdot n_c$ **(8)**, the routine vaccination will be further penalized in the assessment by the regulator. Equation **(8)** can be interpreted as the economy of scale necessary to help justify investment in a vaccine. The increase in production should lead to a decrease in production costs large enough to ensure that the vaccine cost per unit is less than $s \cdot n_c$ (number of sick individuals) times the cost of the treatment.

Development costs

Our assumption that development costs for vaccines and treatments are similar is justified by empirical data. In 2002, the cost of developing and licensing a vaccine was estimated to reach $700 million [12], which is within the range of that for drugs ($403–$802 million) [13].

Marketing and selling costs

The implied assumption in our model is that the drug and vaccines have the same procurement system and the same professional audience for promotion. If one treatment is sold via detailing to physicians while the other is purchased centrally by the regulator, this assumption will not hold true.

Time horizon

It was assumed that pharmaceutical companies had a time horizon t that exceeded n_c. However, if n_c is large, this assumption may not be valid and that will further reduce the value of routine vaccination.

Factors not taken into account in the model

Our simplified model did not take into account certain parameters in the decision-making. In our model, it was assumed that all eligible individuals could be vaccinated or treated; however, the vaccination and diagnosis rates could be less than 100% and their relative values will influence the investment decision. As in the case of the cost of goods, the relative value of fees for vaccine administration and for diagnosis could also impact on the price acceptable to the regulator and the investment decision. In addition, the efficacy of vaccines tends to decrease over time; for example, some vaccines, such as meningococcal and pertussis vaccines, are known to have low persistence [14, 15]. If waning is assumed, the relative value of vaccines will further decrease.

Vaccination could have additional benefits. If vaccinated individuals prevent the spread of a disease via herd protection, not all susceptible cohorts have to be fully vaccinated to eliminate the disease, leading to a higher economic value of vaccination. The indirect effect (and the duration of protection) can have a substantial impact on vaccines' economically justifiable price [16]. However, herd immunity can only be proven when a large number of individuals are vaccinated. Often, herd immunity is not shown when health authorities recommend a vaccine and implement a vaccination program under systematic surveillance. Therefore, health authorities may or may not assume indirect effects when making a health economic evaluation. For instance, the Joint Committee on Vaccination and Immunisation, when making its interim decision on vaccination against meningitis B, concluded that "current [indirect effects] evidence [was] insufficient to support a recommendation for the introduction of a routine adolescent immunisation programme" [17].

Empirical evidence

Incentives to develop HIV interventions

In the previous sections, we developed a theoretical model to understand the incentives to invest in curative vs. preventive interventions. In this section, the model findings are applied to understand whether economic evaluation methods may (partially) explain the absence of a vaccine to prevent HIV. Numerous reasons to explain this absence have been mentioned in the literature. Scientific challenges are significant [18] but, according to Cohen [19] and Thomas [20], critical causes also include scientific infighting, the lack of co-ordination between institutions, and the lack of funding from pharmaceutical companies. In fact, Harris [21] estimated that in 2008, pharmaceutical companies only invested $33 million in research for an HIV vaccine. For Craddock [22], this inadequate research investment is "because the countries hardest hit by AIDS cannot afford to buy vaccines in quantities adequate to achieve

a minimum profit margin". However, worldwide sales of the HIV therapies[a] recommended by the US Department of Health and Human Services amounted to over $14 billion in 2010 [23]. Therefore, the HIV market cannot be considered unattractive for pharmaceutical companies: some other market incentives must explain the lack of a vaccine.

An alternative argument [21] is that governments will prevent price discrimination between high- and low-income countries, but this argument also applies to preventive medicines and does not specifically disadvantage vaccines. However, it is possible to deduce from Harris [21] that the HIV market is not unattractive to vaccine manufacturers per se, but that instead it is unattractive with respect to vaccines *as compared with* drugs. To test this, we can analyse the HIV market in the US using our framework described above.

As 86% of newly diagnosed HIV cases occur in people aged between 20 and 54 years, we can assume that $n_c \approx 35$ (see Table 3). Using the discount rates from Section 3.3 and assuming that $t = n_c$, the expected revenues from routine vaccination of adolescents will be only 43% of those of a cure. As noted by Harris [21], the prospect of a large catch-up campaign that would favour a vaccine investment seems too unpredictable to motivate substantial R&D investment. If the time horizon used by pharmaceutical companies is only 10 years, the incentive to develop a routine vaccine will even be lower. The annual HIV incidence is approximately 1150 for each 1-year age cohort group (Table 3). Using US population tables, the incidence s is approximately 27 per 100 000 [24], and $n_c \cdot s << 1$. Therefore, the economies of scale have to be very large to help justify a vaccine investment (i.e., $c_1 \ll c_0$).

Scope and use of the model framework

This article is a theoretical article that could apply for diseases not yet preventable by immunization. Those include (but are not limited to) sexually transmitted diseases (AIDS,

chlamydia, gonorrhoea, syphilis, etc.), tuberculosis, malaria, enterotoxic *escherichia coli*, respiratory syncytial virus, group B streptococcus, cytomegalovirus, etc.

The authors could not identify any company that developed a drug over a vaccine (or a vaccine over a drug) within the context of this model, potentially because companies do usually disclose major investment decision but keep the underlying strategic reasons and discussions confidential.

Recommendations for the regulator

Rappuoli et al. [5] and Lattanzi & Rappuoli [25] discussed a number of incentives to favour investment in vaccines. For instance, they recommended that vaccine development should benefit from tax breaks, extension of patent terms, creative use of the orphan drug law, reduction in liability risks, public–private partnerships, etc. Our paper highlights potential additional means to increase the incentives to invest in vaccines. In particular, the regulator could: (i) Choose a long-term horizon when evaluating health technologies (i.e., a high value for t). (ii) Choose a much lower discount rate compared with that used by the manufacturer. (iii) Conduct a catch-up campaign. (iv) Choose a lower discount rate for vaccines than for drugs. (v) Ensure that B_1 exceeds B_0. For regulators using budget-impact models, this means that additional budget should be allocated to vaccines. For regulators using a cost-effectiveness approach, it means that vaccines could be assigned a higher cost-effectiveness threshold to account for the intangible value of vaccines discussed by Masignani et al. [4]. In particular, the impact on productivity for the society as whole [4], utility by anticipation, and the impact on other countries could be taken into account in the evaluation. (vi) Ensure that the costs of developing, producing, and selling the vaccines are lower than those of drugs. This could take the form of central procurement with a guaranteed price to reduce selling costs. Similar to the suggestion of Berman and Giffin [1], it could also be a public–private partnership, such as a grant to develop the vaccine or to finance a manufacturing facility. The

US government followed that path by awarding $60 million over 4 years to Novartis Vaccines and Diagnostics to expand their laboratory facilities and to include a pandemic influenza and emerging-disease centre [26].

The credibility of the regulator's commitment is critical in the process. If this commitment is not perceived as credible by manufacturers, it may not foster vaccine innovation. However, as it takes approximately 10–12 years to bring a vaccine to market, the regulator's commitment needs to be made when the development of the vaccine actually starts. Finally, considering budget cuts, health authorities may be reluctant to engage in large catch-up campaigns once a vaccine is approved.

Conclusions

If no catch-up vaccination campaign is implemented, the expected value to the manufacturer of developing a vaccine is much lower than that of developing a drug, everything else being equal. This can be explained by the fact that with vaccination there is a ramp-up time required to achieve protection of the full population. However, if a catch-up campaign vaccinates all susceptible individuals, the expected revenues from vaccines could exceed those of a treatment (assuming there is no waning in efficacy). If the cost of goods is high for vaccines relative to drugs, vaccination is not likely to be as attractive for manufacturers as a curative treatment would be. This article provides additional tools to those already proposed by academics to increase incentives to invest in vaccines. However, we do not suggest that changing market incentives will necessarily lead to vaccines being developed against all relevant diseases, including HIV. Even within the current evaluation framework, vaccines against relatively rare diseases such as meningitis have been developed, suggesting that existing incentives may already be attractive to some manufacturers. Market incentives do not seem to be the only driving factor; other considerations such as clinical or humanistic arguments are usually also taken into consideration. The probability of clinical success for each type of intervention is undoubtedly crucial: for example, in rapidly progressing diseases in which the onset of the effect of treatment may be too slow once the disease is diagnosed, prevention may be viewed as a better strategy than treatment. Fast-progressing diseases, such as meningitis, may therefore be optimal candidates for a preventative vaccination programme.

Competing interests

The authors are employees of Novartis Vaccines & Diagnostics AG. This paper represents the view of the authors and should not be considered as representative of the view of Novartis Vaccines & Diagnostics AG.

Authors' contributions

SR conceived and developed the model and drafted the manuscript. JH contributed to the design of the model and the drafting of the paper. Both authors have read and approved the final manuscript.

Authors' information

The study reported in this paper was conducted as part of the author's research at the University of Neuchâtel, Switzerland. The author and the co-author are employed by Novartis Vaccines & Diagnostics AG (NVD).

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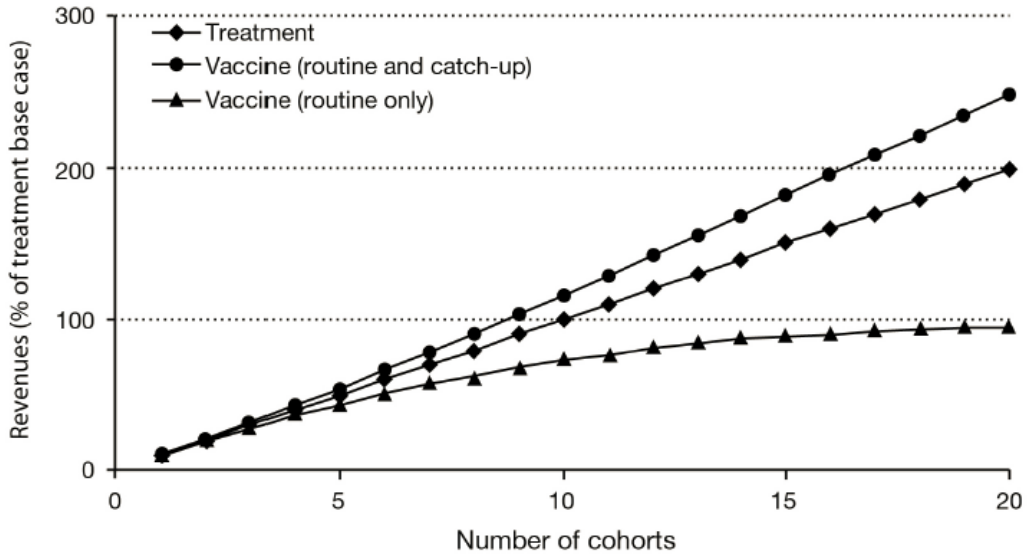
[http://www.cdc.gov/hiv/surveillance/resources/reports/2010report/index.htm]

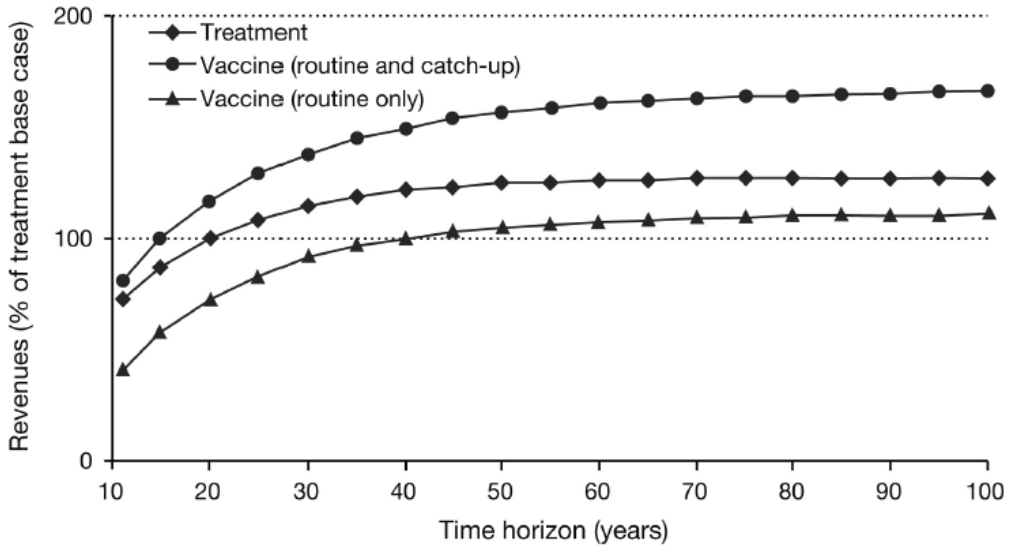
Figure

Figure 1. Impact of the number of cohorts (n_c) on the sales potential.



100% represents the discounted sales generated by the treatment for base case values (e.g., with n_c = 10).

Figure 2. Impact of the time horizon (*t*).



100% represents the discounted sales generated by the treatment for base case values (e.g., with $t = 20$).

Table 1. Summary of terms used in the model

Term	Definition
B	Budget threshold (regulator)
CA_{ji}	Cost avoided with technology j in year i
c_c	Annual cost of the disease per cohort before introduction of a new technology
C_{ji}	Cost associated with developing and selling technology j in year i
d	Number of years after launch used for economic evaluations by the manufacturer
E_{ji}	Incremental quality-adjusted life-years gained from technology j in year i
j	Technology indicator ($j = 0$ for treatment; $j = 1$ for prevention)
l	Number of years required to develop technology before launch
M_{ji}	Gross margin for technology j in year i
t	Time horizon in years used for economic evaluation (regulator)
n_c	Number of cohorts susceptible to the disease
P_{ji}	Price of technology j in year i
Q_{ji}	Quantity (demand) for technology j in year i
r_m	Discount rate used by manufacturer to evaluate investment
r_r	Discount rate used by regulator to evaluate new technologies
s	Annual probability of children in susceptible cohorts becoming sick
S_{ji}	Sales of technology j in year i
$y_t(r)$	Discounting factor in the t^{th} year, if the discount rate is r

Table 2. Evaluation of treatment and prevention

	Treatment (j = 0)	**Prevention (j = 1)**	
Parameter	(A)	Routine and catch-up (B)	Annual routine only (C)
Demand (Q_{ji})	sn_c	n_c if $I = 1$ 1 if $I > 1$	1
Cost avoided (CA_{ji})	$c_c n_c$	$c_c n_c$	$i \cdot c_c$ if $I \leq n_c$ $c_c n_c$ if $I > n_c$
Price (P_j)	$1/(sn_c) \cdot (c_c n_c + B_0)$	$\frac{1+r_r - y_{t-1}(r_r)}{1+n_c r_r - y_{t-1}(r_r)} \times (c_c n_c + B_1)$	$B_1 + c_c \times \frac{1+r_r - y_{n_c-1}(r_r) - n_c r_r y_t(r_r)}{r_r(1 - y_t(r_r))}$
Annual sales (S_{ji})	$(c_c n_c + B_0)$	$P_1 \cdot n_c$ if $i=1$ P_1 if $i>1$	$B_1 + c_c \times \frac{1+r_r - y_{n_c-1}(r_r) - n_c r_r y_t(r_r)}{r_r(1 - y_t(r_r))}$
Total revenues[a]	$\frac{1 - y_t(r_m)}{r_m} \times (c_c n_c + B_0)$	$\frac{1 - y_t(r_r)}{r_m} \times \frac{1+r_r}{1+r_m} \times \frac{1+n_c r_m - y_{t-1}(r_m)}{1+n_c r_r - y_{t-1}(r_r)} \times (c_c n_c + B_1)$	$\frac{1 - y_t(r_m)}{r_m} \times P_1$

[a] Manufacturers' revenues discounted from the time of launch until the end of the evaluation. See Table 1 for definitions of symbols.

Table 3. Estimated* number of diagnoses of HIV infection in 2010 [27]

Age at diagnosis (years)	Estimated* number of diagnoses	Percentage of all diagnoses
<13	217	<0.5
13–14	34	<0.1
15–19	2200	5
20–24	7565	16
25–29	6823	14
30–34	5954	13
35–39	5523	12
40–44	5720	12
45–49	5296	11
50–54	3671	8
55–59	2154	5
60–64	1119	2
≥65	853	2

* Estimated numbers resulted from statistical adjustment that accounted for reporting delays and missing risk-factor information.

Additional material

Additional file 1: Appendix with propositions and mathematical proofs

Proposition 1

$$S_t = \sum_{i=1}^{t} \frac{1}{(1+r)^i} = \frac{1 - y_t(r)}{r}$$

Proof:

$$S_t = \sum_{i=1}^{t} q^i = q \times \frac{1 - q^t}{1 - q}$$

If we replace q with $\frac{1}{1+r}$ we get:

$$S_t = \frac{1}{1+r} \times \frac{1 - 1/(1+r)^t}{1 - 1/(1+r)} = \frac{1 - y_t(r)}{r}$$

Proposition 2

$$S_t = \sum_{i=1}^{t} iq^i = \frac{q - (t+1)q^{t+1} + tq^{t+2}}{(1-q)^2}$$

Proof:

$$S_t - qS_t = (1-q)S_t = \sum_{i=1}^{t} iq^i - \sum_{i=1}^{t} iq^{i+1} = \sum_{i=1}^{t} iq^i - \sum_{i=2}^{t+1} (i-1)q^i = \sum_{i=1}^{t} iq^i - \sum_{i=1}^{t+1} (i-1)q^i = \sum_{i=1}^{t} q^i - tq^{t+1} = q\frac{1-q^t}{(1-q)} - tq^{t+1} = \frac{q - (t+1)q^{t+1} + tq^{t+2}}{(1-q)}$$

$$\Rightarrow \quad S_t = \frac{q - (t+1)q^{t+1} + tq^{t+2}}{(1-q)^2}$$

Proposition 3

$$S_t = \sum_{i=1}^{n_c} i\frac{1}{(1+r)^i} + \sum_{i=n_c+1}^{t} n_c \frac{1}{(1+r)^i} = \frac{1+r-y_{n_c-1}(r)-n_c r y_t(r)}{r^2}$$

Proof:

Considering the following series:

$$T_t = \sum_{i=1}^{n_c} iq^i + \sum_{i=n_c+1}^{t} n_c q^i$$

$$T_t - qT_t = \sum_{i=1}^{n_c} iq^i - \sum_{i=1}^{n_c} iq^{i+1} + \sum_{i=n_c+1}^{t} n_c q^i - \sum_{i=n_c+1}^{t} n_c q^{i+1} = \sum_{i=1}^{n_c} iq^i - \sum_{i=2}^{n_c+1}(i-1)q^i + \sum_{i=n_c+1}^{t} n_c q^i - \sum_{i=n_c+2}^{t+1} n_c q^i = \sum_{i=1}^{n_c} q^i - n_c q^{n_c+1} + n_c q^{n_c+1} - n_c q^{t+1} = q\frac{1-q^{n_c}}{(1-q)} - n_c q^{t+1} = \frac{q-q^{n_c+1}-(1-q)n_c q^{t+1}}{(1-q)}$$

$$\Rightarrow T_t = \frac{q-q^{n_c+1}-(1-q)n_c q^{t+1}}{(1-q)^2}$$

If we replace q by $\frac{1}{1+r}$ we get:

$$S_t = \frac{\frac{1}{(1+r)} - \frac{1}{(1+r)^{n_c+1}} - (1-\frac{1}{(1+r)})\times n_c \times \frac{1}{(1+r)^{t+1}}}{(1-\frac{1}{1+r})^2} = \frac{1+r-\frac{1}{(1+r)^{n_c-1}} - r\times n_c \times \frac{1}{(1+r)^t}}{r^2} = \frac{1+r-y_{n_c-1}(r)-r\times n_c \times y_t(r)}{r^2}$$

Proposition 4a

The maximal achievable price for routine immunization combined with catch-up in the first year is:

$$P_1 = \frac{1 + r_r - y_{t-1}(r_r)}{1 + n_c r_r - y_{t-1}(r_r)} \times (c_c n_c + B_1)$$

Proof:

$Q_{1i} = n_c$ if $i = 1$ and $Q_{1i} = 1$ if $i > 1$, $CA_{1i} = c_c n_c$ which, by updating equation **(1)** leads to:

$$\frac{n_c P_1 - n_c c_c - B_1}{(1 + r_r)} + \sum_{i=2}^{t} \frac{P_1 - n_c c_c - B_1}{(1 + r_r)^i} \leq 0 \Leftrightarrow \frac{(n_c - 1)P_1}{(1 + r_r)} + \sum_{i=1}^{t} \frac{P_1 - n_c c_c - B_1}{(1 + r_r)^i} \leq 0$$

From Proposition 1:

$$\frac{(n_c - 1)P_1}{(1 + r_r)} + (P_1 - n_c c_c - B_1) \times \frac{1 - y_t(r_r)}{r_r} \leq 0$$

Multiplying with $(1 + r_r) \times r_r$ leads to:

$$(n_c - 1) \times r_r \times P_1 + P_1 \times (1 + r_r) \times (1 - y_t(r_r)) \leq (n_c c_c + B_1) \times (1 + r_r) \times (1 - y_t(r_r))$$

Since $(1 + r_r) \times (1 - y_t(r_r)) = (1 + r_r - y_{t-1}(r_r))$,

$$(n_c - 1) \times r_r \times P_1 + P_1 \times (1 + r_r - y_{t-1}(r_r)) \leq (n_c c_c + B_1) \times (1 + r_r - y_{t-1}(r_r))$$

The maximal acceptable price for the regulator is:

$$(n_c c_c + B_1) \times \frac{1 + r_r - y_{t-1}(r_r)}{1 + n_c r_r - y_{t-1}(r_r)}$$

Proposition 4b

The discounted revenue (from the manufacturer's perspective) for routine immunization combined with catch-up in the first year is:

$$\frac{1-y_t(r_r)}{r_m}\times\frac{1+r_r}{1+r_m}\times\frac{1+n_c r_m - y_{t-1}(r_m)}{1+n_c r_r - y_{t-1}(r_r)}\times(c_c n_c + B_1)$$

Proof:

$Q_{1i} = n_c$ if $i = 1$, otherwise $Q_{1i} = 1$

$$\sum_{i=1}^{t}\frac{Q_{1i}P_{1i}}{(1+r_m)^i} = \frac{n_c - 1}{(1+r_m)}P_1 + \sum_{i=1}^{t}\frac{P_1}{(1+r_m)^i} = P_1\times\frac{1+n_c r_m - r_m y_t(r_m) - y_t(r_m)}{r_m(1+r_m)} = P_1\times\frac{1+n_c r_m - y_{t-1}(r_m)}{r_m(1+r_m)}$$

$$= \frac{1+r_r - y_{t-1}(r_r)}{1+n_c r_r - y_{t-1}(r_r)}\times\frac{1+n_c r_m - y_{t-1}(r_m)}{r_m(1+r_m)}(c_c n_c + B_1) = \frac{(1+r_r)(1-y_t(r_r))}{r_m(1+r_m)}\times\frac{1+n_c r_m - y_{t-1}(r_m)}{1+n_c r_r - y_{t-1}(r_r)}\times(c_c n_c + B_1)$$

Proposition 5

The maximal price for routine immunization is:

$$P_1 = B_1 + c_c \frac{1 + r_r - y_{n_c-1}(r_r) - n_c r_r y_t(r_r)}{r_r(1 - y_t(r_r))}$$

Proof:

$Q_{1i} = 1$, $CA_{1i} = ic_c$ if $i \leq n_c$ and $CA_{1i} = c_c n_c$ if $i > n_c$ leading to an updated equation **(4)**

$$\sum_{i=1}^{n_c} \frac{P_1 - ic_c - B_1}{(1+r_r)^i} + \sum_{i=n_c+1}^{t} \frac{P_1 - c_c n_c - B_1}{(1+r_r)^i} \leq 0$$

which can be rewritten as:

$$\sum_{i=1}^{t} \frac{P_1 - B_1}{(1+r_r)^i} - \sum_{i=n_c+1}^{t} \frac{c_c n_c}{(1+r_r)^i} - \sum_{i=1}^{n_c} \frac{ic_c}{(1+r_r)^i} \leq 0$$

By using Proposition 1 and Proposition 3:

$$(P_1 - B_1)\frac{1 - y_t(r_r)}{r_r} - c_c \frac{1 + r_r - y_{n_c-1}(r_r) - n_c r_r y_t(r_r)}{r_r^2} \leq 0$$

Therefore, the maximal acceptable price is:

$$P_1 = B_1 + c_c \frac{1 + r_r - y_{n_c-1}(r_r) - n_c r_r y_t(r_r)}{r_r(1 - y_t(r_r))}$$

Proposition 6

If $B_1 = B_0 = 0$, the revenues from routine vaccination are asymptotically (i.e., when $t \to +\infty$)

$\frac{(n_c - 1)}{2} \times r_r$ lower than those of treatment.

Proof:

Asymptotically, the discounted revenues are:

$D_0 = \frac{c_c n_c + B_0}{r_m}$ for treatment, and

$D_1^r = \frac{1}{r_m}(B_1 + c_c \frac{1 + r_r - y_{n_c - 1}(r_r)}{r_r})$ for routine vaccination.

Since $y_{n_c - 1}(r_r) = 1 - (n_c - 1) \times r_r + \frac{1}{2}(-n_c + 1).(-n_c) \times r_r^2 + o(r_r^3)$

then $D_1^r \sim_{t \to +\infty} \frac{1}{r_m}(B_1 + c_c n_c - \frac{1}{2}(n_c - 1) n_c c_c r_r)$ if r_r^2 is small.

Therefore, if r_r is small and $B_1 = B_0 = 0$:

$\frac{D_1^r - D_0}{D_0} \sim_{t \to +\infty} - \frac{(n_c - 1)}{2} \times r_r$

Endnotes

[a] Drugs with sales above $100 million in 2010: Atripla ($2927 million), Truvada ($2746 million), Reyataz ($1479 million), Kaletra ($1255 million), Isentress ($1090 million), Prezista ($888 million), Epzicom ($858 million), Combivir ($561 million), Norvir ($344 million), Sustiva ($315 million), Viramune ($295 million), Intelence ($243 million), Trizivir ($223 million), Crixivan ($206 million), Epivir ($178 million), Ziagen ($159 million), Selzentry ($124 million), Viracept ($112 million); values from EvaluatePharma [23].