The Costs and Benefits of Front-loading and
Predictability of Immunization
By Owen Barder and Ethan Yeh

Abstract

How can the international community save more children's lives faster and more effectively in the 21st century? This Working Paper analyzes the extent to which "frontloading" and predictable vaccine funding, as proposed by the International Finance Facility for Immunization (IFFIm), is more effective in impacting vaccine coverage than spending vaccine funds equally throughout the lives of projects. The IFFIm is an initiative of the Global Alliance for Vaccines and Immunization (GAVI), and supported by the governments of the United Kingdom, France, Sweden, Italy, Spain and Norway. An initial IFFIm investment of $4 billion is expected to prevent 5 million child deaths by 2015, and more than 5 million future adult deaths. Using a stylized model, the authors quantify the positive and negative effects of predictable vaccine funds and frontloading, and finds IFFIm's approach can increase the impact of vaccine coverage by 22%. This is because stable and long-term financing allows vaccine manufacturers and countries to plan for long periods of time, knowing that resources will be available. Front-loading helps to reduce the spread of disease and to immunize large groups of people faster.

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The costs and benefits of front-loading and predictability of immunization*

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Summary

This paper estimates in stylized form the potential economic benefits of allowing spending on vaccines to be made more predictable, and of 'front-loading' spending to allow immunization to be scaled up more rapidly. [1] For the purposes of this paper, 'front-loading' is defined as changing the phasing of a program so that it uses the same total inputs, but uses them more quickly so that outputs are realized sooner.

The proposed International Finance Facility for Immunization (IFFIm) to increase spending on improving health systems and vaccines is one mechanism that could allow spending on vaccines to be front-loaded and more predictable. [2] This paper does not analyze the financial mechanism proposed for IFFIm.

The focus of our analysis is to compare the extent to which predictable and front-loaded spending, as opposed to spending the same resources year to year, can impact vaccine coverage and health benefits. It is *not* our objective to validate previous estimates of the health benefits of the proposed increase in spending under IFFIm, but rather to analyze the extent to which those health benefits are affected by making the spending predictable and front-loaded.

Immunization is generally recognized to be one of the most cost-effective development interventions. [3] The UK Government quotes WHO estimates that additional spending of about $4bn would save the lives of more than 5 million children over the 10 year period, and would save a further 5 million future adult deaths as a result of hepatitis B immunization. [4] This paper considers whether the benefits of front-loading and predictability of spending on vaccines are likely to exceed the financial costs.

We estimate that the overall health impact of spending on vaccines could be increased by about 22 percent by making the spending front-loaded and predictable, even after taking into account the additional costs of private sector borrowing. [5] Predictability adds about 11 percent to the health impact of spending, and front-loading adds an additional 10 percent. (These two effects multiply together to make 22 percent in total) [6]

Table 1: Summary of estimated benefits of same total spending under alternative scenarios

Scenario	I	II	III
	No front loading unpredictable	No front loading predictable	Front loading predictable
a. Donor country contributions	$4,475m	$4,475m	$4,475m
b. Developing country contributions	$1,074m	$1,074m	$1,074m
c. Net cost of financing from front-loading	-	-	$150m
d. Spending on vaccines and health services (a + b – c – all in NPV $2005)	$5,549m	$5,549m	$5,399m
Life-years gained [7]	175 million	194 million	214 million
Cost per life-year gained ($ / DALY) [8]	$31	$28	$25
Health benefits as a percent of Scenario I	100%	111%	122%

The cost-effectiveness of vaccines as a development intervention

Immunization has been one of the most important successes in public health during the last 40 years. The Expanded Programme on Immunization (EPI) was launched by the World Health Assembly in 1974, aimed at increasing coverage of vaccines against six diseases (tuberculosis, diphtheria, neonatal tetanus, whooping cough, poliomyelitis and measles).[9] Globally, coverage with three doses of the Diphtheria-Tetanus-Pertussis vaccine (DTP3) was increased from less than 5 percent in the early 1970s to 75 percent by 1990; it fell during the 1990s to 72 percent in 1999; and by 2003 was back up to 78 percent.[10]

As a result of these vaccinations, an estimated 3 million lives are saved each year, and an additional 750 000 children are saved from permanent disability.[11] In 1993, the World Bank concluded that the six EPI vaccines together with hepatitis B vaccine, yellow fever and vitamin supplements ("EPI plus") were among the most cost-effective health interventions for developing countries, ranging from US$16-22 per DALY gained in low income countries and US$ 33-39 per DALY gained in middle income countries.[12] Table 2 below sets out some estimates of the cost-effectiveness of vaccination in particular contexts. Note that the newer vaccines are currently more expensive than the older vaccines, and are therefore likely to be less cost-effective per DALY saved.

Table 2. Estimates of cost-effectiveness of vaccination

Immunization	Cost DALY saved (US$)	Source[13]
Measles	<11.7 (2-15)	Foster *et al.* in Jamison *et al.* 1993
EPI cluster: polio, DPT, BCG, measles: Low-income	14-20	Jamison *et al.* 1993
EPI cluster: polio, DPT, BCG, measles: Mid-income	29-41	Jamison *et al.* 1993
Hepatitis B Low-income countries, prevalence less than 2%	42-59	Miller, McCann 2000
Hepatitis B Low-income countries, prevalence greater than 8 per cent	8-11	Miller, McCann 2000
Hib (Africa)	21-22	Miller, McCann 2000
Hib (low-income Asia)	55	Miller, 1998

By way of comparison, Table 3 below sets out estimates of the cost per DALY of a selection of other health interventions in developing countries. As a guide to judging cost-effectiveness, development interventions are generally considered to be highly cost effective if the cost per DALY is less than $100.[14] More recently, a country's annual GDP per capita has been used as a benchmark.[15] In the United States, the cost-effectiveness threshold is estimated to be $50,000 to $100,000 per DALY saved.[16] In the United Kingdom, the decisions of the National Institute for Clinical Excellence are consistent with an implicit cost effectiveness threshold of about £30,000 ($50,000) per DALY saved.[17]

Table 3: Cost per DALY of other health interventions[18]

Condition	Cost per DALY	Source
Tuberculosis		
Directly observed short therapy for smear positive patients	<$40	CMH Working Group 5: Paper 8
Bacillus Calmette-Guerin (BCG) vaccine	<$50	
Directly observed short therapy for smear negative patients	$10 to $20	
HIV/AIDS		
Condom distribution	$1-$100	Creese 2002
Improved Blood Safety	$1-$43	
Prevention of Mother-to-child transmission (nevirapine)	$1-12	
Peer Education for commercial sex workers	$4-7	
Highly active anti retroviral therapy	$1,100 to $1,800	
Malaria		
Insecticide treated bednets	$19 to 85	Goodman, Coleman and Mills (2000)
Residual spraying	$16 to $29	
Chaemoprophylaxis for children	$8 to $41	

The need for improved immunization coverage

Vaccines have been successful in greatly reducing the burden of diphtheria, pertussis, tetanus, polio and measles. However, measles, pertussis, hepatitis B, diseases related to *Haemophilus influenzae* type b (Hib) and tuberculosis remain significant causes of death and disability, as shown in Table 4 below.

Approximately 1.2 million people die each year of diseases which are preventable by the six basic vaccines of the EPI program. At least a further 2-3 million deaths a year could be avoided by full use of more recently-introduced vaccines, such as those which protect against Hib and Hepatitis B, and new vaccines which protect against rotavirus and pneumococcal diseases.[19] The expansion of vaccination in developing countries, both by increasing coverage for existing vaccines and by extending the use of new vaccines, to reduce these preventable deaths is a cost-effective way to reduce mortality and morbidity in developing countries. Increasing immunization is likely to make an indispensable contribution to achieving the fourth Millennium Development Goal, to reduce the rate of under-5 mortality by two-thirds between 1990 and 2015.[20]

Table 3: Annual vaccine preventable deaths[21]

Annual deaths (000s)	Under 5	Total
Diseases for which vaccination is part of the EPI schedule		
Measles	540	610
Pertussis	294	294
Tetanus	198	213
Diphtheria	4	5
Polio	<1	<1
Other diseases for which vaccination is part of some countries' vaccination schedules		
Yellow Fever	15	30
Hib	386	386
Hepatitis B	<1	600
Diseases for which a licensed vaccine is available but not yet widely used		
Japanese encephalitis	5	14
Meningococcal	10	26
Rotavirus	402	449
Pneumococcal	716	1612
Total	**2,572**	**4,240**

Constraints on vaccine coverage and use

There are two related causes of vaccine preventable deaths. First, 22% of the world's children do not fully receive the basic package of childhood vaccinations; second, many of the children who receive those do not receive other, more expensive vaccines.[22] Vaccination rates are lowest in poor countries, and among the poor in middle-income countries. The key constraints to greater vaccination coverage are:

- **Financial barriers**
  High vaccine prices remain an important barrier to the adoption of new vaccines. Even in countries that can reach the majority of their children with cheaper vaccines – such as DTP (Diphtheria-Tetanus-Pertussis) and OPV (Oral Polio Vaccine)– there are many children who do not receive the relatively expensive vaccines for Hib, and, to a lesser extent, Hepatitis B and Yellow Fever. This is only partly the result of insufficient coverage of immunization systems: in some cases the price of immunizing every child with all of these vaccines is too large to be accommodated within current health budgets in developing countries. GAVI has made significant progress in addressing financing constraints, but total resources are still insufficient and most donors are willing to commit funds only for a relatively short period. Developing country health ministries are understandably reluctant to introduce new vaccines or extend immunization infrastructure without a clear picture of long-term sustainability of vaccine supply. This is a particular challenge at present as the first set of GAVI grant recipients are reaching the end of their funding.

- **Delivery capacity**
  Health systems need to be able to manage a comprehensive immunization strategy, including obtaining safe and effective vaccines, storage, logistics (including a cold-chain), waste disposal, social mobilization and communication, monitoring and evaluation, training staff to administer vaccines safely and managing adverse events. Substantial investments are needed to extend the reach of

vaccination to more children. However, for a given level of vaccine coverage, the cost of adding another vaccine to the set of vaccines given to children who are already being immunized is generally relatively modest, if those vaccines can be administered in the same visit. As a result the cost effectiveness of investment in immunization infrastructure increases as the number of vaccines that are delivered to each child during a visit increases.

- **Procurement and planning constraints**
  Ineffective demand forecasting, lack of coordination, lack of disease data and needs assessments, inability to enter into long term purchasing arrangements all contribute to higher prices than could be achieved with more predictable procurement, and lead to occasional supply shortages. (The Accelerated Development and Introduction Plans (ADIPs) for rotavirus and pneumococcus aim to address many of these constraints for these two diseases.[23])

- **Inadequate monitoring and surveillance**
  Accurate monitoring and surveillance data are essential for good management of service delivery and for early warnings of outbreaks. These efforts depend on capacity in remote areas, as well as central managerial and analytical capacity.

Additional funding would both allow greater vaccine purchases and more investment in health systems to broaden coverage. Additional funding can also make an important contribution to complementary improvements in health system management to allow improved forecasting, monitoring and surveillance.

The IFF for Immunization (IFFIm)

GAVI proposes to increase the resources available for childhood vaccines in GAVI-eligible countries over the coming years, by seeking long term donor pledges which they can securitize and use to front-load funding for vaccination programs. According to GAVI,[24] this will allow both developing countries and vaccine manufacturers to plan for longer periods of time knowing the necessary resources will be available. This is expected to secure better pricing, accelerate increased availability of new vaccines, and support the substantial system improvements required to absorb new vaccines such as pneumococcal and rotavirus. The goal is to scale up coverage to 90% in every country, in accordance with the goals set in the World Fit for Children declaration in 2002.

The IFFIm proposal seeks financing of over $4 billion over 10 years. According to the project documentation, this is intended to supplement GAVI support to increase routine coverage in the 30 GAVI eligible countries to 90% by 2015, compared with the current average of 50%.[25] The programme is estimated to have the potential to save an estimated 5.3 million lives in the years to 2015, and prevent a future five million adult deaths that would otherwise be caused by hepatitis B in adulthood, in addition to the 1.5 million deaths that could be prevented if support for the Global Alliances for Vaccines and Immunisation (GAVI) continues at its current level of resources.[26] The UK Department for International Development estimates that the benefit:cost ratio of this spending on vaccines would be over 10:1 (at a real discount rate of 3.5%), and the NPV of the programme as a whole would be $60bn.[27] The analysis recognises that there are risks that weak absorptive capacity might undermine the effectiveness of the program, but notes that half the proposed resources are for system strengthening and that most of the barriers to expanded immunisation at local and community level are amenable to being dealt with through increased financial resources.

In addition to providing additional spending, the IFFIm proposal suggests that the productivity of spending on vaccines and health systems can be increased by (a) front-loading the spending; and (b) making the spending more predictable:

The focus of our analysis is to compare the extent to which predictable and front-loaded spending, as opposed to spending the same resources spread evenly and without predictability, can impact vaccine coverage and health benefits. It is *not* our objective to validate previous estimates of the health benefits of the proposed increase in spending under IFFIm, but rather to analyze the extent to which those health benefits are affected by making the spending predictable and front-loaded.

The IFFIm Financial Mechanism

This section, which is drawn from the IFFIm proposal and accompanying analysis, explains the financial mechanism underlying IFFIm. To achieve predictability and front-loading, IFFIm envisages the establishment of a mechanism to borrow from private capital markets, on the basis of donor commitments of future spending. This would provide funds which can be programmed (and if necessary committed) in advance, and which can be spent sooner (that is, front-loaded).

Diagram 1: Frontloading of IFFIm financing
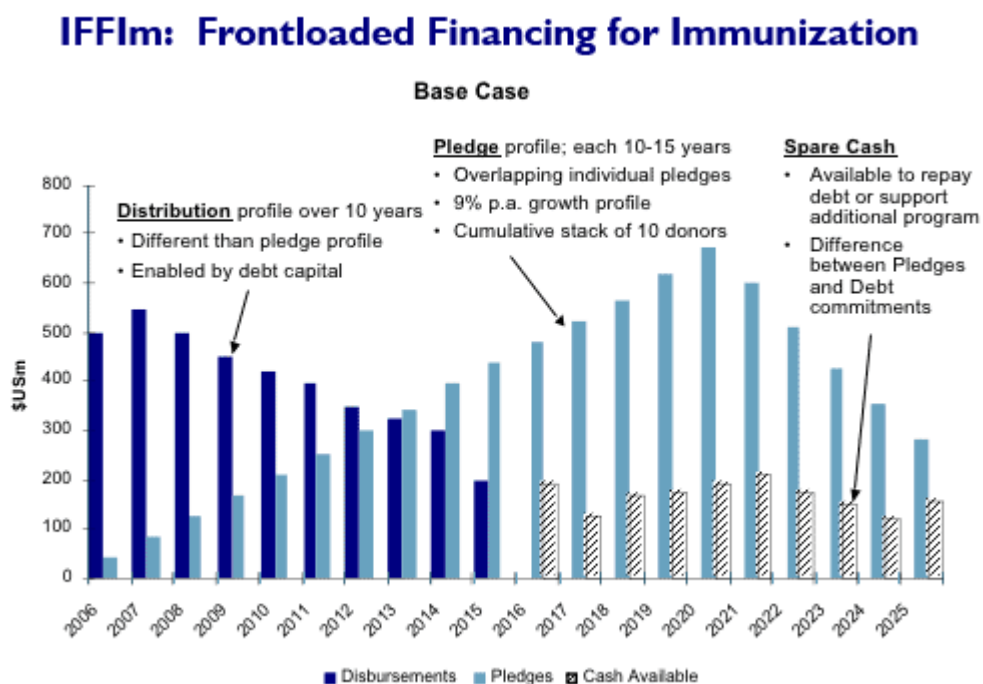
Source: GAVI[29]

There is a cost to borrowing money, namely interest costs and financial transactions costs. Analytically, this gives rise to the question of whether the benefits of front-loading and predictability are greater or less than the costs resulting from the interest and transactions costs of borrowing the money. For this proposal to be preferable to existing mechanisms for funding immunization programs, the benefits of predictability and front-loading would need to exceed the financial costs.

It is not within the scope of this paper to analyze the financial mechanism proposed for the IFFIm. We have taken as given the estimated financial costs of borrowing under IFFIm as a benchmark against which to

compare our estimates of the benefits of predictability and front-loading. Clearly, if there are other ways to achieve these benefits but which involve lower financial costs, that would be better value for money.

Theoretical consideration of the costs and benefits of predictability and front-loading

This section considers the benefits and costs of predictability and front-loading from a theoretical perspective. The following section then considers the approximate size of these effects, using an empirical model.

The theoretical benefits of predictability

The **first expected benefit of predictability** is increasing the likelihood of **investment by firms in larger-scale production capacity** and reducing vaccine prices if they have more certainty about future demand. Appendix A sets out the economic theory supporting this, and uses a simple empirical example to illustrate the potential magnitude of these effects.[30] The analysis shows that it may be in both the firms' and the buyers' interests for there to be more certainty about future vaccine demand before the firm invests in production capacity.

If vaccine procurement is unpredictable, and if contracts cannot be agreed to in advance, firms have to determine what quantity to produce several years before the price and quantity is agreed to with the purchasers. (A vaccine manufacturing plant costs about $¼-½ billion, and has a lead time of 3 years or more.[31]) In these circumstances it may not be rational for a firm to invest in large-scale capacity sufficient to serve the needs of the developing world, because once the firm has sunk investment in this capacity, it bears the risk that the vaccines it can produce will not be bought. An investment by a firm in large-scale capacity may weaken its negotiating position when it subsequently tries to agree to a price and quantity with buyers (there are few outside markets for high volumes of vaccine). Because firms foresee that they will not have a strong hand in negotiations once the plant is built, they have little incentive to invest in large-scale production unless they have obtained a commitment on the price they will obtain for their products. So even though there are very large returns to scale in vaccine production, it is not in the firm's interest to build a large vaccine plant unless they have prior commitments on price and quantity.

The quantified analysis in Appendix A shows that agreements to buy vaccines before a firm builds a production plant would likely result in much more cost-effective contracts for purchasers, and so larger health benefits for a given budget. In our hypothetical example, the expected number of vaccines purchased could be increased by 50 percent if donors would agree to quantity and price in advance. Put another way, if donors insist on "keeping their options open", they are likely to have a choice among options which all entail higher vaccine prices than if they are prepared to limit their future discretion by negotiating a contract in advance. Such contracts are only possible if spending on vaccines is sufficiently predictable for purchasers to enter into long-term, predictable contracts.

Significant price reductions are likely mainly for those vaccines for which there are not yet a large number of competing manufacturers, and which are currently considerably more expensive than the established vaccines such as DTP and OPV.

The **second expected benefit of predictability** is that it will allow the governments and health service managers of developing countries to **make investments to increase coverage**. Developing countries, and their donor partners, sometimes hesitate about investing in infrastructure for vaccine delivery, including training, logistics, cold-chain, public awareness and outreach, if the future flow of vaccines at affordable prices is uncertain. For example, one reason for the low rates of roll-out of both Hepatitis B and Hib in the past decade has been uncertainty about the prospects for affordable supply of these vaccines when the transitional funding provided by GAVI runs out. More predictable funding would enable countries to make long-term, informed choices about which products they want to introduce into their vaccination schedule and when, to make appropriate arrangements for investments in health service infrastructure and to budget for their co-payments for vaccine procurement.

The **third expected benefit of predictability** is that it enables investments to be planned and phased to achieve the **most efficient use of resources over time**. If budgets for health service improvements and the purchase of vaccines are decided from year to year, then there will inevitably be an *ad hoc* allocation each year between systems investments and vaccine procurement. If future funds for vaccine procurement are more reliable, by contrast, then spending can be programmed over time to invest first in health systems and increased coverage, and then in the vaccines that can be delivered through those enhanced systems. More efficient vaccination, for example through greater use of routine immunization and lower dependence on one-off campaigns, can increase the cost-effectiveness of spending on immunization. [32]

The anticipated costs of predictability

The **main expected cost of greater predictability** is that there is some risk that donors will be committed to making payments in the future which, when the time comes, either no longer represent the donor's political priorities, or which are **no longer the most cost-effective available intervention.** For example, more cost-effective alternatives may become available or new diseases may emerge which are higher priorities. However, vaccination has a long record as a very cost-effective and effective development intervention, so the risk is small that donors would find themselves committed to investments in vaccination that they would no longer want to make.

The **second expected cost of predictability** is that the **legislative and administrative arrangements for expenditure commitments** may prevent donors from making commitments, or they could only do so with very high transaction costs. The extent of this cost varies from one jurisdiction to another, and if there is sufficient political will the obstacles to these commitments can be overcome. IFFIm is one way in which donors can make spending more predictable and front-loaded, and we have used this mechanism as the basis of our estimates of the benefits front-loading and predictability.

The anticipated benefits of front-loading

Three main benefits are anticipated from front-loading of spending on health systems and the purchase of vaccines: reducing the disease epidemic, increased economic benefits, and greater predictability for suppliers.

The **first expected benefit of front-loading** is on **the impact of the disease burden**. As we show in a simplified model, for some (but not all) diseases, immunization benefits not only the vaccinated individual, whose risk of catching the disease is reduced, but also other people who come into contact with that individual as the population risk of catching the disease is also reduced. This effect is called "herd immunity".

The most extreme form of this benefit is apparent for those diseases which can be eradicated altogether, such as smallpox and perhaps polio. Smallpox was eradicated in 1980, after a 15 year campaign led by the World Health Organization (WHO). The total cost of eradication of the disease was $300 million. It has been estimated that the United States saves the total cost of all its contributions to the eradication of smallpox every 26 days. [33]

Disease eradication is a limiting case of the more general spill-over benefit to one individual of vaccination of another. Suppose that, at the margin, a government can afford to vaccinate two individuals, and it can choose whether to vaccinate them both this year, both next year, or one each year. In most cases, it will be better to vaccinate them both this year, as not only will two individuals benefit from vaccination, but other members of the population will benefit both this year and next from a lower risk of catching the disease. If the vaccinations are spread evenly, the total herd immunity benefits for the population are less than if the vaccinations are front-loaded. However, as coverage rates increase to very high levels, the additional benefits of herd immunity fall, because there are fewer susceptible people in the population to benefit. The optimal level of vaccination depends on, among other things, the characteristics of the disease and of the population.

Herd immunity effects have been demonstrated for vaccines against diseases such as pertussis, typhoid and yellow fever, and for both oral and inactivated polio vaccines. [34] For other vaccines, especially those which

have little effect on disease transmission, such as BCG and tetanus, there is thought to be little or no herd-immunity benefit from vaccination.

The **second expected benefit of front-loading** is that there are likely to be **continuing economic and fiscal benefits** to the recipient country from lower levels of disease. A front-loaded program will realize these benefits more quickly. These include higher productivity and lower costs to health services resulting from disease. Substantial empirical evidence suggests that health is a key determinant of productivity and economic growth.[35] Futhermore, high levels of mortality can lead to low levels of saving and investment, and hence low levels of economic growth. One recent study found that high adult mortality in Africa can statistically account for all of Africa's growth shortfall since 1960.[36] In principle, it is also likely that the cost of vaccinating future cohorts of children might be financed largely by future savings in health care costs, which result from today's vaccination. Because the benefits are a future stream of higher economic activity and lower health costs throughout the lifetime of the protected cohort, a front-loaded vaccination program could generate larger benefits over time than a program which is spread over time.

The **third benefit of front-loading** is that it could add to the **predictability of the spending on the vaccination program**. While firms may respond positively to longer term procurement contracts which could be available under predictable funding, they may discount future revenues to take account of the perceived risk of default. Front-loading the revenues provides immediate payments rather than the promise of future payments, and so further reduces the risk to firms. In principle, this should reduce the price at which firms are willing to sell vaccines. Note that this is an additional effect over and above the benefits of predictability through long-term contracting.

There is a **fourth, more technical, benefit of front-loading**, which is included in our estimates. In line with convention (though not uncontroversially), we discount future DALYs saved at a discount rate of 3% a year. This reflects **the principle that future benefits are less valuable than benefits achieved today**.[37] It means that the total estimated health benefits of vaccinations administered over 20 years are lower than the benefits of the same number of vaccinations administered over 15 years, other things being equal. (Note that if the annual cost of finance is broadly comparable to the discount rate on future benefits then, other things being equal, the benefits of bringing forward a fixed amount of health gains would approximately equal the financial costs of doing so.)

It is important to recognize that front-loading resources will not deliver all of the health benefits outlined above if the addition of financial resources will not alleviate the binding constraints vaccination coverage For example, if inadequate health infrastructure is the main reason why some children are not vaccinated with all the available vaccines, and some are not vaccinated at all, and if the health infrastructure could not be improved if more money were available, then frontloading of expenditure would not result in the benefits described here. In our model, based on the original IFFIm proposal, about half the additional spending is allocated to improving health systems to improve vaccine coverage, based on extrapolations from detailed estimates of the costs of increasing coverage.

The anticipated costs of front-loading

The **principal cost of front-loading is the financial cost**. In principle, donors could choose to re-phase their spending on support for vaccinations, making those commitments predictable *without* specific borrowing. For example, donors can re-phase spending within existing budgetary allocations. This spending would be implicitly financed by additional government borrowing which would typically be cheaper than borrowing from the private sector. In practice, budgetary constraints or administrative arrangements in some donor countries make it unlikely or impossible for them to change the profile of their spending in this way.

Rather than public borrowing, the IFFIm proposal is to establish a Special Purpose Vehicle company, IFFIm Co, which would borrow money in commercial markets, using the donor commitments as security. IFFIm Co could then use that capital to make spending both front-loaded and predictable.

This private borrowing will incur interest and financial transactions costs. The total additional cost of private borrowing is represented by the difference between the net present value of the total stream of

expenditure commitments and the net present value of the total stream of disbursements. As shown in Table 4 below, the Department for International Development estimates that the additional financing costs resulting from private borrowing will be 3.5 percent of the total expenditure.[38] This can be regarded as the net cost of front-loading in a context in which front-loading is possible only through borrowing from the private sector.

Table 4: Key Financial Aggregates for the IFFIm Model Base case

Aggregate	Amount
(1) Undiscounted cash value of IFFIm pledges	$7,345m
(2) Undiscounted cash value of IFFIm disbursements	$4,000m
(3) Additional disbursements from cash cushion (assuming no default)	$1,694m
(4) Total cash value of interest payments	$1,650m
(5) Total cash value of IFFIm costs and other fees	$93m
(6) NPV of disbursements and 'spare cash'	$4,325m
(7) NPV of pledges (including IFFIm fees)	$4,475m
(8) Difference between (6) and (7)	$150m
(9) (8) as a % of (6)	3.5%
Source: Department for International Development (2005)	

A **second expected cost of front-loading** is that the **marginal cost of vaccinating an additional child in each country is likely to increase as total vaccine coverage in that country increases**. The costs of vaccinating children at low vaccine coverage levels tend to be lower because those children are easily reached are have easy access to health clinics or facilities. The costs at high vaccine coverage levels increase greatly because those harder to reach children often live in more geographically remote areas or may be more socially excluded. (Marginal costs may fall as coverage increases when coverage is low because of returns to scale; however, costs of reaching additional children increase again when coverage is high because of the cost of reaching the most remote or excluded children.[39])

If vaccinations are front-loaded, then average coverage rates would be higher than if the same number of vaccinations were delivered over a longer time. With increasing marginal costs, these higher coverage rates may imply higher average costs and hence, for a fixed total of additional spending, lower immunization rates than if the spending is not front-loaded.

A possible **third cost of front-loading** could be that vaccine prices would be higher, on average. This might happen if the prices of vaccines (especially of new vaccines) are expected to fall over the years under consideration, so concentrating more of the purchases in the early years will increase the average price paid. In addition, prices might actually *increase* temporarily as a result of the expansion of demand caused by front-loading (with supply inelastic in the short term). For example, the additional demand for vaccines that followed the creation of the Global Alliance for Vaccines and Immunization may have contributed to the increase in Hib vaccine prices.[40] This effect emphasizes the importance of ensuring that front-loading and predictability are introduced together. Front-loading without increasing predictability might actually reduce the cost-effectiveness of vaccine purchases if it drives up short term vaccine prices.

Assessing the relative size of the costs and benefits of predictability and front-loading

We used a spreadsheet model to estimate the relative size of these various effects and so determine whether the benefits of predictable and front-loaded spending on vaccines are likely to exceed the financing costs. (For the purposes of comparison with the estimated benefits, we have used the estimated financing costs of IFFIm as the basis of comparison, but the results are applicable however front-loading is financed.)

To do this, we adapted the models of vaccination coverage and costs originally created by the World Health Organization for the purpose of estimating the effects of the IFFIm program. This was not the purpose for which the models were originally developed, and our approach is limited by a number of simplifications and assumptions that we have made. We have organized the models in a form which enables us to estimate the impact of changes in the amount and timing of spending on vaccination coverage and health benefits.

Changes in vaccine coverage as a result of changes in spending are calculated by country. The coverage rates are then aggregated into WHO 14 sub-regions to calculate health benefits, which are based on our extrapolations from WHO estimates of DALYs lost in 2002.[41] DALYs saved are calculated by multiplying the number of people vaccinated in a cohort, the efficacy of the vaccine, and our estimate of the lifetime DALY burden per person for that disease in that sub-region, based on the WHO estimates of actual DALYs lost in 2002. This estimates the total DALYs saved for that cohort. Future DALYs saved are discounted to 2005 at an annual rate of 3 percent.

An outline of the structure of our model is shown in the diagram below.

Figure 1: Diagram of Spreadsheet Model
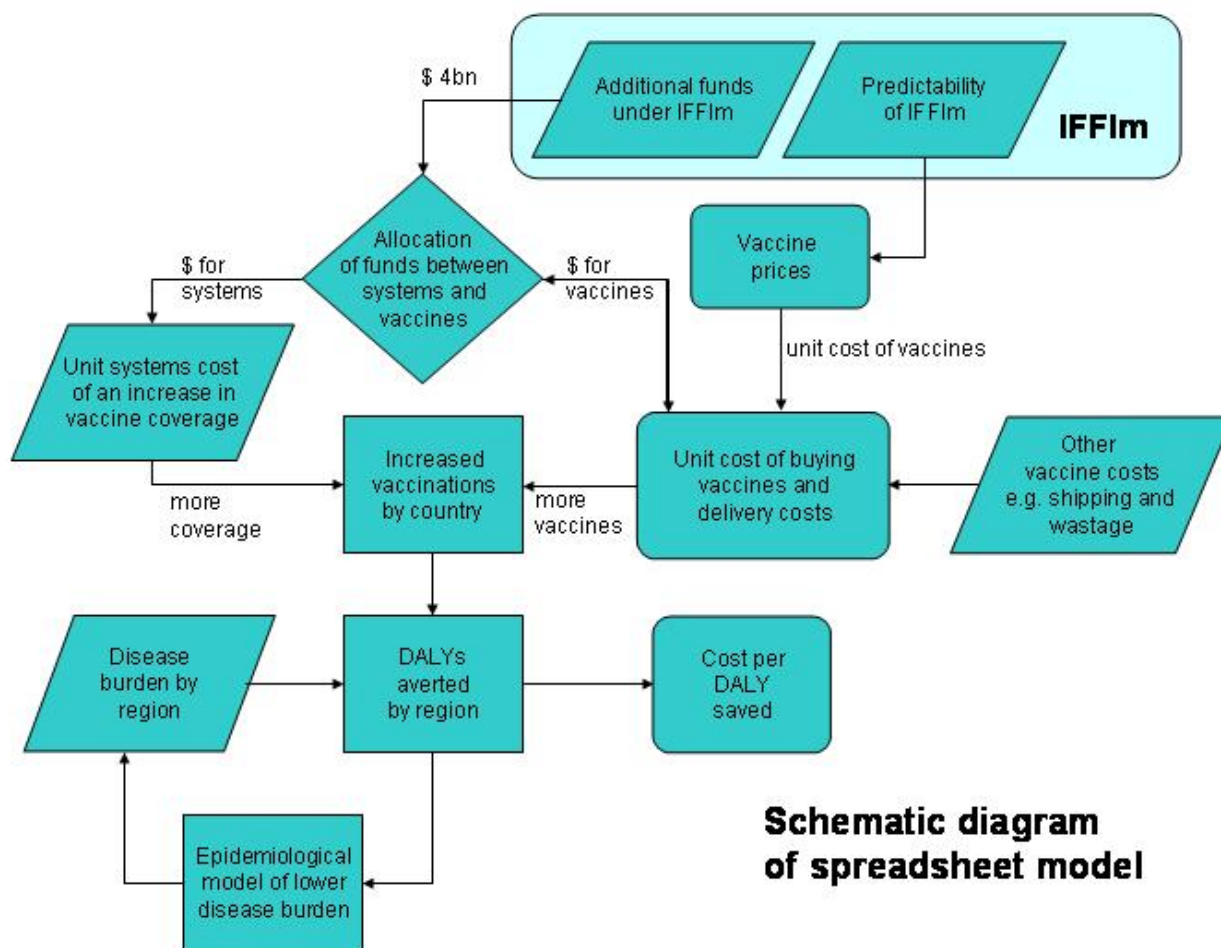
Comparison of three scenarios

To identify the impact of front loading and predictability, we compared three different scenarios, set out in Table 5 below.

Table 5: Comparison of three scenarios

Scenario	I	II	III
Descriptions	No front loading unpredictable	No front loading predictable	Front loading predictable
End year	2020	2020	2015
Spending on vaccines and health services ($m)	$4,475m	$4,475m	$4,325m
Financing costs ($m)	$0m	$0m	$150m
Total donor contribution ($m)	$4,475m	$4,475m	$4,475m
Comparison of scenarios	Predictability ⟩	Front loading ⟩	

Broadly speaking, a comparison of Scenario I and Scenario II provides an estimate of the benefits of greater predictability; while a comparison of Scenario II and Scenario III provides an estimate of the benefits of front-loading, assuming predictability. (Scenario III is meant to be broadly equivalent to the IFFIm proposal.)

We have kept the total additional spending on vaccines and systems the same in all three scenarios in NPV terms, for the purposes of comparison between the scenarios. No assumption is made in any scenario about the evolution of spending at the end of the period (ie after 15 years in scenarios I and II, and 10 years in scenario III) as we measure only the lifetime benefits to the cohorts of children born over the next 15 years. Clearly, in the real world, steps would need to be taken to ensure that there is no precipitate fall in funding at the end of 10 or 15 years, both because such a fall would deny the benefits of vaccination to future generations, and because the anticipation of such a fall would have an impact on behavior before the end of the period (e.g. on vaccine production volumes, prices, infrastructure investment, and public acceptance of the vaccination program).

The actual use of additional vaccine funding would in practice depend on countries' own analysis of their needs in the circumstances of the time. Furthermore, estimates of the impact of the additional spending on coverage, and the impact of additional vaccination on the disease burden, are necessarily highly uncertain. Given these uncertainties, our goal is not to validate previous cost-effectiveness estimates of vaccination; rather, by using a common set of assumptions about spending choices and potential impact for comparing the three scenarios, our aim is to identify and isolate the specific impacts of predictability and front-loading by comparison with a similar magnitude of spending on vaccines without predictability or front-loading. (One limitation of this approach is that the estimated benefits of front-loading are estimates that also assume predictability.)

The realization of health benefits depends on the ability of countries to build up health systems sufficiently to deliver additional vaccines and to extend vaccine coverage. The additional resources required for health systems to allow this to happen are explicitly included in the model developed to analyze the IFFIm proposal, and we have followed a similar approach. While additional resources needed to improve health systems are explicitly included, it is assumed that there are no other constraints that cannot be lifted through the provision of financial resources. This assumption is reasonable if there is a sufficiently flexible mechanism for allocating resources so that that vaccines are supplied where they can be used, and investments are made to overcome bottlenecks in country health systems.

To estimate **Scenario III** we have followed as closely as possible the estimates of the costs and benefits of the IFFIm package as set out in the GAVI proposal. We are most grateful to the WHO Department of Immunization, Vaccines and Biologicals for the access they have granted us to their data and models that

they use to analyze the likely impact of policy measures. Our spreadsheet model seeks to replicate the WHO approach where possible, but makes a large number of assumptions to simplify the analysis. For example, our estimates of the benefits of increased vaccination coverage depend on sub-regional, not country, level estimates of the burden of disease. Furthermore, whereas the WHO model first estimates possible scenarios for improving coverage (taking into account a range of barriers, not just financial) and then derives the costs of increasing coverage, our model works in reverse, deriving the implied coverage improvements that could be achieved at different levels of investment (assuming that the non-financial barriers to increased coverage are unchanged between the scenarios).

To estimate **Scenario II (predictable but no front-loading)**, our model assumes that the total donor spending is spread over 15 years instead of 10 years. The NPV of the spending is unchanged. There are no longer any direct financing costs, and these resources are instead allocated to systems delivery and vaccines. The funds are allocated geographically, and by disease, in the same proportions and trajectory as the spending in Scenario III. In effect, we have simply stretched the spending profiles for Scenario III over 15 years instead of 10.

To estimate **Scenario I (not predictable and no front loading)**, we adapt Scenario II to take account of the impact of higher vaccine prices for new and underused vaccines resulting from lack of predictability, which reduces coverage. As a result of these higher prices, coverage of all the new and underused vaccines is lower.

Other important assumptions

We have made a number of simplifying assumptions:

- the estimated benefits are calculated over the lifetime of the cohorts vaccinated during the program rather than on a yearly basis;

- the estimated benefits do not include any benefits to later cohorts (e.g. herd immunity benefits to later cohorts of a lower incidence of disease; or benefits to subsequent cohorts from having a better infrastructure in place);

- the total expenditure, including financing costs, is assumed to have the same net present value in all scenarios;

- the benefits of reduced mortality and morbidity are assumed to be additive across diseases.

- we have assumed that there is no change in the number and timing of campaigns against measles, and tetanus, and that the health benefits of these campaigns are unchanged in all scenarios. We have not included herd immunity benefits from campaigns, except to the extent to which they are indirectly included in the estimates of DALYs occurring in 2002 on which our benefit estimates are based.

 A more detailed account of our assumptions is set out in Appendix C.

Table 6: Summary of effects and inclusion in model

Effects of predictability and front-loading	Is this effect captured in the model?
Advantages of predictability	
+ Lower vaccine prices	Yes
+ Investments to increase coverage	Yes
+ More efficient use of health resources	No
Disadvantages of predictability	
- Risk that donors are committed to vaccination and it is no longer cost-effective	No
- Expensive arrangements needed to facilitate predictability	Yes
Advantages of frontloading	
+ Herd immunity	Yes (approximately)
+ Long term economic benefits from earlier reduction in disease; health care costs averted	No
+ Adds to predictability of contracts and so reduces prices	Yes
+ Discounting of future DALYs	Yes
Disadvantages of frontloading	
- Financial costs of front loading	Yes
- Increased average costs of vaccination	Yes
- Higher vaccine prices if contracts not predictable	Yes

Limitations

Our estimates are based on a stylized model and there is a significant margin of error. Estimates of the disease burden, vaccine prices, delivery costs, and the cost of increasing vaccine coverage are all highly uncertain. We attach significantly greater weight to the comparisons *between* scenarios than we do to the total health benefits estimated for each scenario.

The scenarios did not attempt to estimate some effects which might affect the relationship between the scenarios. We did **not** include:

- any long run differences arising from changes in variables at the end of the scenarios; for example on systems coverage, long run vaccine prices or the incidence of disease burden;

- possible increases in investment in research and development on new vaccines which might result from larger and more predictable donor spending on vaccines;

- improved efficiency of investment in health systems resulting from more carefully planned spending;

These effects would be likely to increase the benefits of front-loading and predictability, and so our results may understate the effects of moving from conventional financing to front-loaded and predictable financing.

We take as given the UK Department for International Development's estimate of the financing costs of IFFIm. We have not considered a hypothetical alternative scenario, in which donors find a way to make their commitments predictable and front-loaded, but without requiring private sector borrowing (for example, by rephasing their budgeted expenditure plans, and making administrative arrangements to commit that spending in advance). Any scenario in which the benefits of front-loading and predictability can be achieved without incurring the financial costs of private sector borrowing will represent better value for money than a second-best solution in which those benefits are obtained with the cost of borrowing from the private sector.

Estimating herd immunity

As set out in Appendix B, even quite simple epidemiological models of disease exhibit highly complex, non-linear dynamics which make it very difficult to estimate the trajectory of herd-immunity effects. Because vaccination is generally highly-cost effective even without including the benefits of herd immunity, many estimates of the cost effectiveness of vaccination either ignore these effects altogether, or make only simplified assumptions. This produces conservative estimates of vaccination cost-effectiveness, but excluding these effects may also understate the value of front-loading a vaccination program.

Our approach, set out in more detail in Appendix B, has been to use a simplified generic model for all diseases, but to exclude the dynamic terms of the equations. These dynamic terms can be large, but the variation terms of the equation have zero mean, which means that they cancel each other out over a large number of years. By excluding these, our simplified model does not have predictive power for the level of the disease burden in any one year, but provides a very broad estimate of the impact on disease burden over a number of years taken together.

The price impact of predictability

Both theory and a simple empirical calibration, set out in Appendix A, suggest more predictable procurement of vaccines would lead to a reduction in prices, especially for new and underused vaccines, and that this price reduction might be substantial. In particular, we find that both buyers and producers are likely to be better off if demand is more predictable, because firms can invest in the appropriate size of production facilities, so increasing volumes and reducing prices. Buyers benefit from cheaper vaccines, and firms can make larger returns, than if buyers reserve the right to negotiate on prices and quantities after the production facilities are built.

We have not sought to model the outcome of the negotiation between suppliers and procurement agencies at different levels of demand and predictability. To estimate the likely impact of predictability on vaccine prices, we have instead used scenarios for the price of pentavalent vaccines prepared for the GAVI December 2004 Board Meeting.[42] The price levels in these various scenarios have been discussed – but not necessarily agreed – with various stakeholders in the vaccine supply community. The way in which these assumptions have been used is explained in Appendix A. The benefits of predictability on vaccines are assumed to be confined to new and underused vaccines, such as Hepatitis B, Hib, but not for well-established vaccines that are already produced in large volumes such as DTP and OPV. The estimated reductions in price using this approach are of the same order of magnitude as those predicted by a McKinsey study for the GAVI Financial Task Force.[43]

Our model assumes that purchasing authorities make use of greater predictability of financing by entering into specific long term supply contracts. In other words, it is not enough merely that there is an increased likelihood of spending in the future on vaccines in general, or even on vaccines that protect against a particular disease. For the reasons set out in Appendix A, the really large reductions in vaccine prices depend on the purchasers' willingness to enter into specific supply contracts, for an agreed price and volume of vaccine, in advance.

Chart 1: Assumed price trajectory for pentavalent vaccine under different scenarios
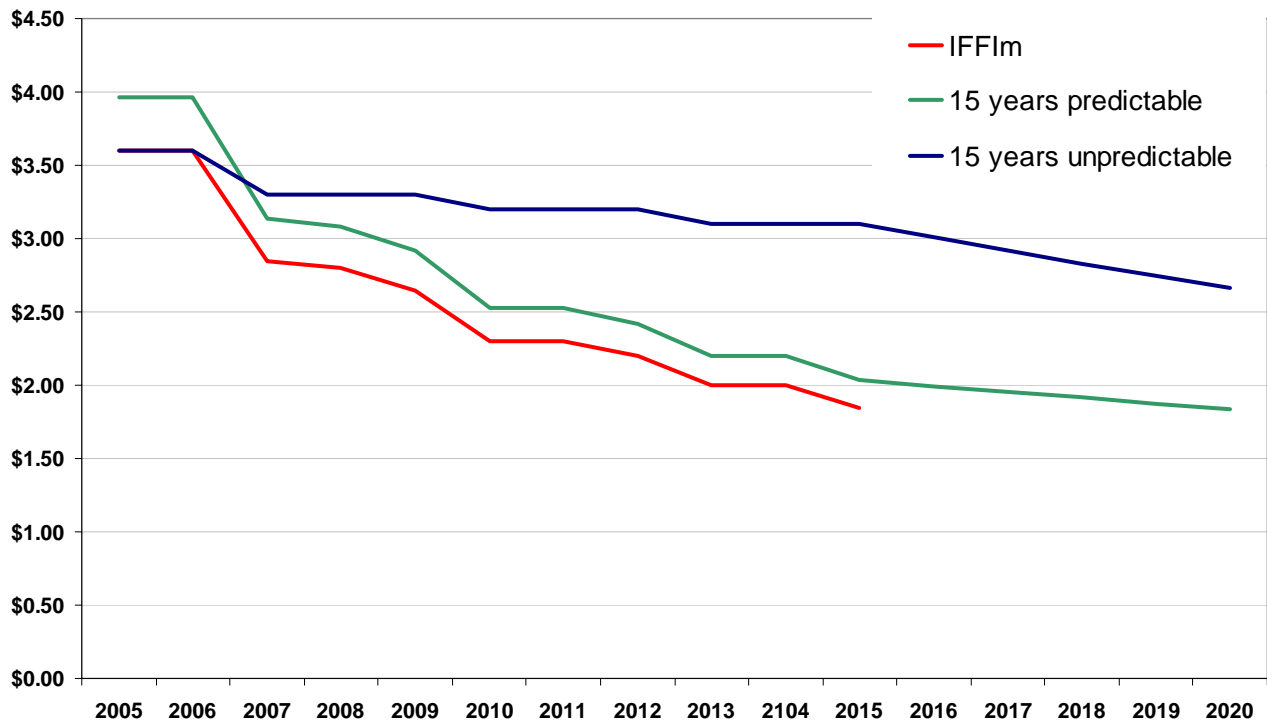

Vaccine coverage

In the front-loaded scenario, vaccine coverage is higher for the first ten years, but the additional spending is assumed for the purposes of this analysis to end in 2016. In all scenarios, expenditure is expected to return to the current, baseline level of spending at the end of the period. (This assumption, which may not be realistic, ensures that we compare the same total expenditure in all three scenarios.)

Figure 2 below shows the estimated effect on coverage for hepatitis B predicted by our model. As expected, the coverage is, as expected, significantly higher over the first 10 years than in a scenario in which the same spending is spread over 15 years. Comparing the fifteen year scenarios, coverage is slightly higher when spending is predictable, because vaccine prices are lower and hence a larger number of children can be vaccinated.

Figure 2: Hepatitis B vaccine coverage in three scenarios[44]
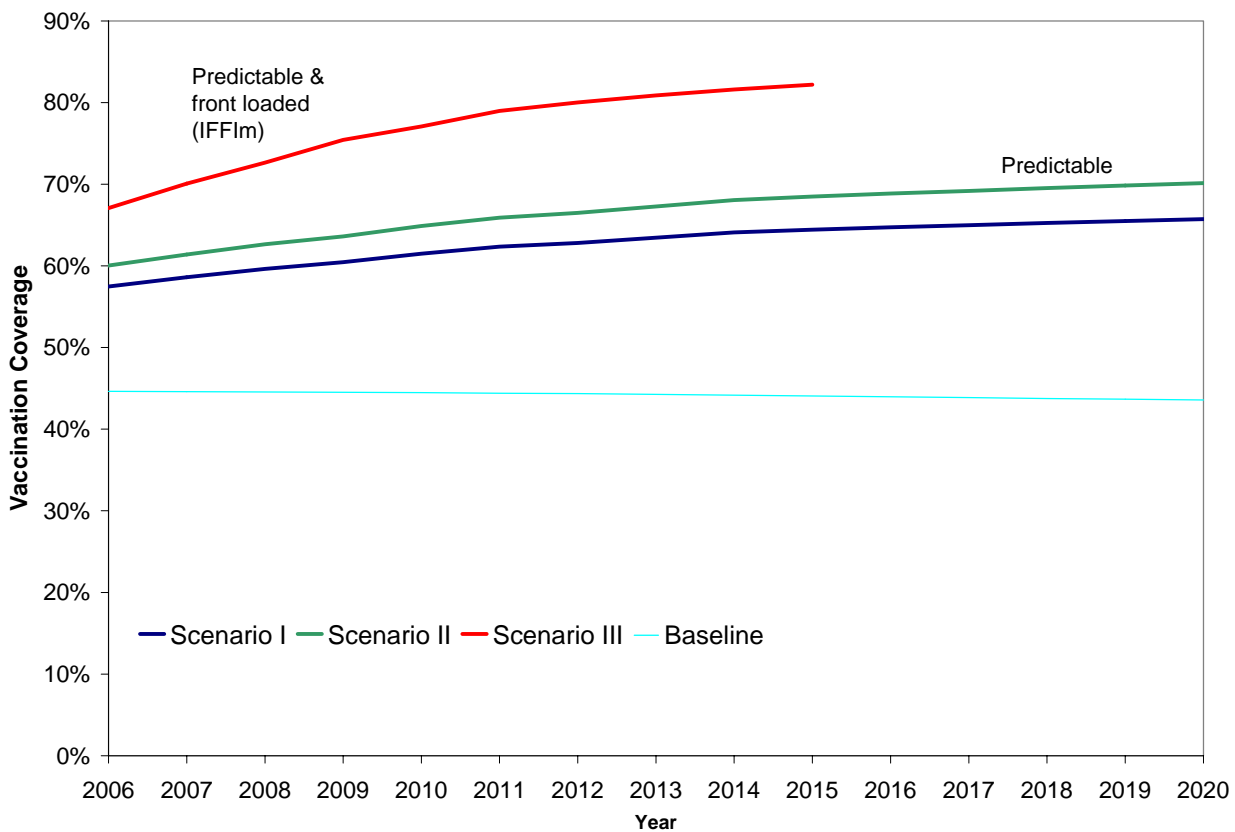
Results: health benefits

Our estimates find that there are likely to be significant overall health benefits from both predictability and from front-loading of spending.

We find that predictability makes a very significant difference, increasing the impact of the program (measured as total DALYs saved) by 11 percent. The main reason for this is the fall in prices of new vaccines that is anticipated if donors are able to enter into long term commitments and predictable procurement, which enables more vaccines to be purchased for a given amount of spending. While the exact size of the fall in prices is highly uncertain, both vaccine producers and purchasers would benefit from greater certainty in vaccine procurement.

We find that front-loading also makes a very substantial difference, improving the impact of the program by an additional 10 percent. This is the result of price effects, herd-immunity effects, and the discounting of future benefits.

Taken together, our stylized model estimates that predictability and front-loading as proposed in the IFFIm would increase the health impact of spending on immunization by some 22 percent (measured as discounted DALYs saved), even taking into account the costs of financing. The benefits of predictability and front-loading are an order of magnitude higher than the additional financial costs from front-loading, which are estimated at 3.5% of the net present value of the total outlays.

Sensitivity to assumptions

We have run the model under a variety of different scenarios, summarized in Table 7 below:

Table 7: Summary of model variants: DALY losses averted under each scenario

Variants	I	II	III	II / I	III / II	III / I
Discounted DALY losses averted	No front loading unpredictable	No front loading predictable	Front loading predictable	Effect of predictability	Effect of front-loading	Combined effect
Main scenario	175 million	194 million	214 million	11%	10%	22%
1. No herd immunity	138 million	157 million	159 million	14%	1%	15%
2. No discounting of future DALYs saved	221 million	246 million	258 million	11%	5%	17%
3. Smaller fall in vaccine prices due to predictability (10% rather than 20%)	175 million	192 million	212 million	10%	10%	21%
4. No price effect from front-loading	175 million	194 million	209 million	11%	8%	19%
5. Overall spending decreased to $3bn	139 million	154 million	169 million	11%	10%	22%
6. Constant marginal delivery costs	182 million	201 million	221 million	10%	10%	21%
7. Double extra financing costs to $300m	175 million	194 million	210 million	11%	8%	19%

A research agenda

These are, at best, broad estimates, based on an extension of the framework for analyzing IFFIm which was developed by the WHO. We believe that this analysis gives reasonable approximation of the orders of magnitude, but that it should initiate further analysis. Over a longer period of time, additional items could be adapted within this framework to extend the analysis:

- a more formal **model of the impact of predictability** and front-loading on vaccine prices, perhaps using a game theoretic model of bargaining between a monopolistic or oligopolistic supplier with a monopsonist buyer;

- **disease-specific models of herd-immunity**, perhaps with less simplified dynamic effects;

- a more detailed model of how additional funds for immunization are **allocated across countries and diseases**, in order to secure the largest possible benefit, rather than maintaining the proportions assumed in the IFFIm programme;

- a model of **health care costs averted**, which we expect would strengthen the case for front-loading of investment in vaccines.

The estimates presented here of the impact of predictability and front-loading are likely to be conservative, in part to avoid overstating the case for front-loading and predictability. We anticipate that the more detailed analyses suggested here would tend to increase, rather than reduce, the estimates of the benefits for front-loading and predictability.

Conclusions

There are strong theoretical reasons for thinking that predictability and front-loading would have both positive and negative effects on the cost-effectiveness of immunization programs. Using a stylized empirical model, we have attempted to quantify the magnitudes of these effects.

We estimate conservatively that the impact of the International Finance Facility for Immunization might be increased by 22 percent as a result of predictability and front loading over using the same funds in a different way. Predictability alone would increase the impact by 11 percent if long term procurement contracts could be agreed. Front-loading was estimated to increase the health benefits of vaccination by an additional 10 percent.

Though our estimates are subject to wide margins of error, the benefits of front-loading and predictability appear significantly to outweigh the financial costs. Our sensitivity analysis shows that this conclusion is robust to a range of assumptions.

We therefore conclude that the effectiveness of spending on immunization programs would be significantly increased by arrangements which enable spending to be predictable and front-loaded, even after allowing for the costs of private borrowing.

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Appendix A: The effect of predictability on vaccine prices

The market for vaccines has a number of characteristics that are important determinants of vaccine prices:

- Vaccine production is characterized by high fixed costs and low variable costs. Mercer Consulting estimates that, for a given plant, variable costs make up 15% or less of the total cost of vaccine production; and significantly less than this if R&D and marketing costs are included.[45] There are thus **significant economies of scale**: if production volumes double, the cost-per-vaccine is significantly reduced, by close to 50 percent.

- There are **barriers to entry** which prevent new producers from entering the market. These include intellectual property rights and trade secrets, manufacturing complexity, and regulatory requirements. The result is that producers have a period of market exclusivity of ten to twenty years. (Vaccines are generally harder markets for generic manufacturers to enter than non-biological pharmaceuticals, because the process of manufacture is more complex, harder to copy, and subject to regulatory approval.)

- There are **long lead times** between investment and production. Investment in production facilities is made 3-5 years before vaccines are produced; research and development, and regulatory approval, might take ten to twenty years.

- Most vaccines are purchased on behalf of developing countries by international procurement agencies such as UNICEF and PAHO. These near monopsonies create **significant market power for purchasers** who seek lower prices to maximize the value of money for scarce health resources.

- Because UNICEF and PAHO depend on funding from donors as well as demand forecasts, they are typically unable to enter into long term contracts. Purchases depend on the availability of donor funding, which is not predictable. **Vaccine demand is therefore variable and uncertain**.

As we shall see below, this combination of characteristics creates market conditions in which rational behavior by producers and purchasers can lead to a sub-optimal equilibrium, which could be improved for both parties if contracts could be signed before the firm decides on the plant size. This is a typical outcome of investment under uncertainty which is characteristic of industries in which there are significant returns to scale and in which investment decisions are made before the price is agreed, such as power generation and telecoms networks.[46]

Theoretical predictions of the impact on vaccine prices

Without long term commitments, this market is likely to lead to insufficient investment, low capacity, higher prices, and low volumes, for two reasons.

First, **uncertainty about future demand creates a risk for producers**. Investment in greater production capacity may lead to substantially lower unit costs of vaccines in the future. The cost of this investment – which may be hundreds of millions of dollars – are borne by producers. If the benefits – in the form of lower vaccine prices – mainly accrue to the purchasers, then it may not be optimal for the producer to make this investment.

The following hypothetical example illustrates the problem. Buyers (eg donors) are assumed to want to spend either $2m a year or $1m a year on a particular vaccine, and each is equally probable. The firm has to decide how big a plant to build before they know how much the buyers are willing to spend. A larger plant costs more to build, but results in lower unit costs and lower prices. If a large plant is built and demand is high, the firm gets a higher profit and buyers benefit from lower prices. But if a large plant is built and demand is low, then the firm faces low profits, or even losses, because they cannot recoup the cost of the investment.

Table A1: Illustration of the effect of demand uncertainty

Scenario	Big plant		Small plant	
	High demand	Low demand	High demand	Low demand
Expenditure	**$2,000,000**	**$1,000,000**	**$2,000,000**	**$1,000,000**
Quantity	**10,000,000**	**2,857,143**	**6,666,667**	**2,222,222**
Price	**$0.20**	**$0.35**	**$0.30**	**$0.45**
Investment (amortized)	$500,000	$500,000	$200,000	$200,000
Variable cost ($)	$0.10	$0.10	$0.20	$0.20
Fixed cost ($)	$0.05	$0.18	$0.03	$0.09
Total unit cost ($)	$0.15	$0.28	$0.23	$0.29
Revenue	$2,000,000	$1,000,000	$2,000,000	$1,000,000
Total cost	$1,500,000	$785,714	$1,533,333	$644,444
Profit ($)	$500,000	$214,286	$466,667	$355,556
Expected profit ($)	**$357,000**		**$411,000**	

(Note: hypothetical figures based on conversations with industry representatives.)

In this example, if the plant size has to be chosen before demand is announced, the firm will invest in a smaller plant, because the expected profit is higher. This is true even for a risk-neutral firm (as is assumed here) because of the structure of costs of vaccine production.

If demand is determined in advance of investment in plant size, the firm will build a small plant if demand is low, and a large plant if demand is high. As the table below shows, the expected result of this sequence is better for both the firm and the buyers.

Table A2: Illustrative payoff matrix: everyone better off if demand determined first

	Plant size determined first	Demand determined first
Expected profit for firm	$411K	$428K
Expected price of vaccines	$0.38	$0.33
Expected quantity of vaccines purchased	4.4m	6.1m

In other words, in this illustrative example, if firms and buyers can agree on the level of demand **before** investment in plant is made, the result would be lower prices, higher quantities of vaccines purchased and used, and higher profits for firms, than if the firm has to invest in production before demand is determined.

The **second** reason why demand uncertainty leads to low investment in production and higher prices is that **prices are set through a negotiation between a producer with market exclusivity and a buyer with market power.** The economics of negotiations between bilateral monopolies is complex: the equilibrium price and quantity can vary significantly, depending on the bargaining strength of each side. This in turn is related to each side's "outside option" – that is, whether buyers have an alternative way to spend their money, and whether sellers could sell their production to somebody else. When a producer sinks a large investment in a vaccine plant without having a contract with the buyers, they gamble that they will be able to recoup these costs through sales. When the producer and buyers subsequently negotiate prices and quantities for the vaccine, the investment in plant and in R&D are **sunk costs**. This means that the producer is always better off selling vaccines if the price is above marginal cost than allowing the deal to fall through, even if this fails to recoup the full cost of their investment. The buyers are aware of this, and can use their bargaining power to drive the price down towards marginal cost. Although the buyers may not be able to buy this particular vaccine elsewhere, they can choose to buy vaccines for a different disease, which will also have health benefits, so they

have a relatively strong negotiating position. A firm with capacity to produce vaccines sufficient to meet a significant share of global demand, by contrast, has nobody else to sell to. As a result, prices tend to fall towards marginal costs, and firms have little prospect of recovering the fixed costs of their investments.

When deciding how big a plant to build, therefore, producers anticipate that a larger plant would produce more vaccines at lower unit costs, but that prices would fall commensurately so that the buyers, rather than the producer, will secure the benefits of returns to scale. If the producer expects prices to fall to around marginal costs, so that they do not recoup their investment, then the effect for them of investing in a bigger plant is that they make a bigger overall loss. Furthermore, if the producer builds a larger plant, and the volume of production increases, their scope for selling their production at the margin to other buyers (*e.g.* rich country governments) is reduced. This reduces their bargaining power in negotiations with the bulk procurement agencies. A rational firm may therefore decide not to make the investment in large volume production, with the result that prices and volumes are higher.

The strategic bargaining outcome is significantly altered if the price and quantity are negotiated before the investment in production is decided. At this stage, the producer has a stronger negotiating position: the investment in production facilities are not yet sunk costs, and so if the buyers wish to secure larger volumes and lower prices, they will have to make an offer to producers which is sufficiently attractive to persuade the producer to invest in a larger plant.

In summary, there are two theoretical considerations which suggest that there would be significant benefits from making demand for vaccines more predictable, both for buyers, who benefit from lower prices and higher volumes, and for firms who benefit from higher profits. First, uncertainty of demand means that a profit-maximizing producer would invest in a smaller plant, rather than risk a large investment on which they may not earn a sufficient return. This effect is caused by the shape of the cost curve, not by risk aversion on the part of the firm. Second, if price and quantity are only negotiated once investment costs are sunk, producers have less incentive to invest in large plants as their bargaining power – which is reduced as plant size increases – is likely to be less than the buyers', resulting in an inability to recover costs through sales.

This analysis shows that it is unlikely to be sensible for buyers to "keep their options open" to decide how much vaccine to buy when vaccines are needed. They would be better off if they eschew the option to negotiate the best possible price once the vaccine plant is built. In the simple quantified example above, the expected number of vaccines purchased could be increased by 50 percent if donors would specify demand in advance of production facilities being built.

Estimating the size of the gains from predictability

The discussion above suggests that there are good theoretical reasons for thinking that there are gains for both producers and buyers from increasing the predictability of demand, by allowing producers to invest in large production plants.

It is difficult to be certain how large these gains might be. In principle, they could be very significant: returns to scale in vaccine production are very large – so building a plant that can produce twice as many vaccines could result in unit costs falling by around a half.

Modeling these gains is hampered by two constraints:

- we cannot observe the cost structure of vaccine production;

- it is technically complex to model bargaining between a monopoly supplier and monopsony buyer; it requires a game theoretic approach, as opposed to estimating a supply curve and demand curve, and the equilibrium depends on estimates of the value of outside options, reputation effects, degrees of market exclusivity, and other determinants of bargaining power.

We have instead sought to estimate the likely impact of predictability on vaccine prices using scenarios for the price of pentavalent vaccines prepared for the GAVI Board.[47] These scenarios use price assumptions

based on demand quantities and projected number of manufacturers becoming WHO pre-qualified. The price levels in the various scenarios have been discussed among the vaccine supply community, but they have not been agreed to with manufacturers. Their purpose is to illustrate different projected pricing trends.

For the purposes of Scenario III, the IFFIm scenario which includes both front-loading and predictability, we have assumed that the price trajectory for pentavalent vaccine[48] is consistent with the GAVI high volume scenario, in which pentavalent vaccine is introduced throughout sub-Saharan Africa, the Middle East and Asia by around 2010, leading to demand of 130 million doses a year. On this scenario, the price is predicted to drop below $2.00.

For Scenario I, which does not assume predictability, we assume more limited investment in production capacity, which we assume is consistent with the medium demand scenario of about 50 million doses of pentavalent per year.

For Scenario II, in which demand is predictable but spending is not front-loaded, we have assumed that prices are will be slightly higher than Scenario III, which front-loads the payments. This difference reflects the likelihood that, even if demand is predictable, firms will still discount future revenues to the extent that they perceive some risk that buyers will change their policies in the future. We have therefore assumed a price trajectory which is 5% above the prices in Scenario III. (This price trajectory does not match one of the GAVI price scenarios; instead it assumes prices which are slightly higher than the low price scenario.)

In order to project the prices for monovalent Hib and Hepatitis B vaccines, we assumed that the prices of individual vaccines adjust so that the cost of the pentavalent vaccine is equivalent to the combined cost of DTP, Hib and Hepatitis B separately. The resulting price trajectories are shown in Chart 1 on page 17.

For simplicity, predictability is assumed to lower the prices for HepB, MCV2, and yellow fever vaccines by 20%. There is no additional reduction in these prices from front-loading. Thus, Hib is the only vaccine which has a price reduction under front-loading.

Finally, we assumed that there is no significant difference for prices of well-established vaccines such as OPV and DTP, which are already very cheap, as these are produced in large volumes at low prices, with a large number of suppliers able to enter the market.

Predictability and prices: conclusion

Vaccine prices may be characterized as a prisoners' dilemma problem, in which both parties are worse off as a result of lack of ability to commit in advance. There would be scope for significant benefits to both buyers and sellers if demand and prices were agreed to before production investment takes place through some type of commitment mechanism. Theory tells us that these benefits may be large – of the order of price reductions of 50% or more.

In order to estimate these effects for the purpose of the current analysis, we have relied on GAVI estimates of the impact on prices of changes in demand. The differences between these price scenarios probably understate the possible benefits of more predictable demand, but they provide a plausible basis for a lower bound of the size of the benefit that might be obtained.

Appendix B: Herd immunity

An SIR model is an epidemiological model that predicts the number of people infected with a contagious illness in a closed population over time. The model gets its name from the fact that it involves equations that link the number of susceptible people, the number of people infected, and the number of people who have recovered and developed immunity to infection. Anderson and May[49] set out a mathematical framework for SIR models. Theoretical models typically use differential or difference equations. Difference equations used for numerical solutions are highly dependent on the units of time chosen.

Even quite simple SIR models based on simple differential equations linking these three categories of people typically exhibit complex, non-linear dynamics, which appear to correspond to complex non-linearities in the evolution of disease epidemics. For our purposes, however, it is the evolution of disease burden over time, rather than the short term dynamics, that are of interest.

In SIR models, a key parameter is R_0, which is the number of people infected by a contact with an infected person in a completely susceptible population, sometimes called the basic reproduction number or epidemiological threshold. If R_0 is less than one, then each person who contracts the disease will infect fewer than one additional person before dying or recovering, and the epidemic will eventually die out. But if R_0 is bigger than one, each person who gets the disease will infect more than one other person, and the epidemic will spread (in the absence of policy interventions).

Assume a simple model in which SIR model, in which the "force of infection", λ, decreases as vaccination rates increases, if the vaccination rate is insufficient to eradicate the disease. In this simple SIR model, the percentage change in disease burden for each cohort as a result of herd immunity is equal to the percentage change in the force of infection.[50]

Assuming type II survival[51] (for ease of calculation) and ignoring dynamic terms, <u>in equilibrium</u>, using equation (5.7) from Anderson & May (1991 p.91):

$$\lambda = \mu . R_0 . (p_c - p) \tag{1}$$

where

μ = a constant (cancels out below)
λ = force of infection
R_0 = basic rate of reproduction for the disease
p_c = critical vaccination proportion = $(1 - 1 / R_0)$
p = proportion of effective vaccination (coverage rate x effectiveness)

- So <u>in equilibrium</u> (from eqn (1)):

$$\theta_t = \lambda'_t / \lambda = \frac{(1 - 1 / R_0 - p'_t)}{(1 - 1 / R_0 - p)} \tag{2}$$

where

θ_t is the change in the force of infection
p' is the effective vaccination rate for current cohort
p is the effective vaccination rate at baseline (whole population)
λ'_t is the force of infection at the higher rate of vaccination
λ is the force of infection at baseline

- Let ε_t = sum of additional people effectively vaccinated under the IFFIm.

$$p'_t = p + \varepsilon_t / N_t \tag{3}$$

where

N_t is the population size

p' is the effective vaccination rate for current cohort

- Then in equilibrium, the estimated change in the burden of disease at time t caused by the increase in vaccinations is given by this multiplier θ_t:

$$\theta_t = \frac{(1 - 1/R_0 - p - \varepsilon_t/N_t)}{(1 - 1/R_0 - p)} \qquad (4)$$

- We can use θ_t as an estimate the change in the burden of disease for the population as a whole resulting from the reduced equilibrium force of infection.

Approximations and assumptions

This approach makes a number of important simplifying assumptions:

- it ignores the complex dynamics of the epidemiological response; even in simple models, the force of infection fluctuates around the long term equilibrium before it settles down, possibly with large amplitude; we ignore this effect, in part because the cumulative lagged effects of an increasing vaccination rate may offset each other, and in part for computational ease;

- it ignores any change in health burden arising from a delay in the onset of disease as a result of increased herd immunity;

- it assumes homogenous, mixing populations;

- it assumes the vaccination rate for the existing stock of population is the current (baseline) vaccination rate (ie it assumes that current vaccination rates have existed for a long time); there are many cases for which this assumption is inaccurate – for example, there have been a significant number of measles campaigns between 1999 and 2005;

- we assume the basic rate of reproduction (R_0) given in Table 4.1 of Anderson and May (p70); and we constrained θ_t to be positive (negative values are possible when R_0 is small and vaccine coverage high).

- the approach would not apply to tetanus, which is not contagious and for which there is therefore no herd immunity; it would apply (with different choice of R_0) to all the other diseases under consideration;

- we have estimated the reduction in the burden of disease (using the multiplier θ_t) for the cohorts that obtain vaccinations under the additional vaccination program, by assuming that each cohort makes up approximately $1/40^{th}$ of the population; but we have not included the reduction in disease resulting from herd immunity for those cohorts born before the additional vaccination begins, nor the reduction for those born after the vaccination program comes to an end; thus, we approximate the term ε_t using the cumulative sum of additional individuals vaccinated under IFFIm (over projected baseline vaccine coverages) in cohorts born between the years of 2006 to 2020; N_t is approximated with 40, a parameter that can also represent the length of herd immunity;

- The effective vaccination rate at baseline for the whole population (in our case, for a sub-region), p, is difficult to determine because each disease has different transmission characteristics and herd immunity effects that depend differently on past routine vaccinations and campaigns; we have thus made the simplifying assumption of approximating p using the baseline vaccination coverage in a particular sub-region in each year (the herd immunity parameter θ_t is calculated each year between 2006 and 2020).

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Appendix C: Other assumptions

1. Most vaccine models specify a coverage rate for a particular vaccine in each country at each point in time and derive the health benefits and amount of required spending. In order to compare the three scenarios in our analysis, we make coverage rates a function of the model instead, using the costs and actual amount of money spent in each of the three scenarios as the main exogenous parameters. To determine the spending patterns, we assume that the allocation of spending across diseases, countries, and time remains proportionally the same in all scenarios. The proportional spending on each vaccine in Scenario 3 follows as closely as possible the coverage rates and costs of the IFFIm package estimated by the WHO Immunization, Vaccines and Biologicals Division, as set out in the IFFIm proposal. The same spending patterns for each vaccine and each country are maintained for the 15 year scenarios and simply spread out proportionally over 15 years.

2. The number of tetanus, yellow fever, Measles Containing Vaccine (MCV) catch-up and MCV follow-up campaigns are assumed to be the same in all scenarios.

3. The total vaccine cost is estimated as (actual cost of each vaccine + freight charge + syringe cost) x required number of doses x 1/(1-wastage rate)

4. Systems costs consist of delivery costs and infrastructure costs. Delivery costs are increasing in population coverage for each country and are specific to the coverage level for a particular vaccine. Delivery costs are derived from the cost per outpatient visit from the WHO-CHOICE website (http://www3.who.int/whosis/cea/prices/unit.cfm?path=whosis,cea,cea_prices,cea_prices_unit&language=english). The delivery costs are treated as marginal costs rather than average costs to obtain coverage rates from available spending. Systems costs are assumed to be a constant proportion (7 percent) of the total delivery cost. No account is taken of lumpiness in systems spending; and systems spending has no benefits in subsequent years (ie it is assumed to be amortized). Systems costs cover routine systems and vaccines. Systems support for the introduction of vaccines is assumed to be 7.2% of IFFIm spending (after any financing costs) in all scenarios.

5. 4.4% of IFFIm spending (after any financing costs) is set aside for polio stockpile in all scenarios. No health benefits are calculated for the stockpile in any scenario. The costs of polio vaccine stockpiles are excluded from the cost per DALY estimates.

6. All figures are expressed in real terms, in 2005 prices.

7. While coverage rates under each scenario are calculated at the country level, disease burden is calculated at the WHO sub-regional level. Where necessary, averages by sub-region (e.g. coverage rates by sub-region) are birth-cohort-weighted averages (or infants-surviving-to-one-year-cohort-weighted averages with vaccines where infants surviving to age one are vaccinated rather than the entire birth cohort) across all countries in the region.

8. The disease burden calculation has discount rates in two places. The "real discount rate" is used to discount future disability-adjusted life years (DALYs) to obtain the discounted average number of DALYs lost due to each disease for a person born in a particular WHO sub-region. This can be thought of as the lifetime burden that would be relieved by vaccination over the lifetime of the typical newly born person in a country. The "discount rate for disease burden" is used to discount future DALYs averted during the length of the proposed IFFIm program (e.g. DALYs saved by vaccinations in 2007 are discounted by a further 3% compared to DALYs saved by vaccination in 2006).

9. Hib and yellow fever DALY data are limited, so the disease burden for those two diseases is estimated. The current DALY burden for Hib is estimated by calculating the relationship between deaths and DALYs for lower respiratory infections, and applying this relationship to the WHO regional estimates of deaths due to Hib. The current DALY burden for yellow fever is estimated by calculating the relationship between deaths and DALYs for dengue fever, and applying this relationship to WHO regional estimates for deaths due to yellow fever.

10. The health benefits of measles, tetanus, and yellow fever campaigns have not been explicitly calculated in the model to simplify the analysis. In order to make the three scenarios comparable, the assumption was made that campaign spending remains the same in all three scenarios. Even if lower coverage levels "trigger" an additional campaign to be required in a country, we have assumed that the funding for the additional campaign does not come from the IFFIm to keep the resource allocation and spending comparable in the three scenarios.

As a result, the direct vaccination benefits (health benefits to those immunized) are roughly equal in all three scenarios because the same number of campaigns are being funded in each country in each scenario. To simplify the analysis, we have not explicitly calculated these direct vaccination benefits, which can vary depending on the age of vaccination. Campaigns attempt to vaccinate a wider age-range of the population, and thus, require additional assumptions of the amount of DALYs saved depending on the age of the person vaccinated. The DALY benefit to each person vaccinated in a campaign may differ substantially from the lifetime DALY burden we calculate in the model for a vaccinated infant. Since we had already assumed that the same number of campaigns in each country were being funded in all three scenarios, we simplified the analysis by not calculating health benefits of campaigns.

For purposes of better comparing the magnitudes between the three scenarios, we have made a conservative assumption that campaigns result in approximately 27 million DALYs averted in each scenario. It is likely that campaigns will have greater herd immunity benefits in Scenario III when spending is both predictable and front-loaded because higher vaccination coverage levels are reached. Adding 27 million DALYs saved to each scenario therefore under-estimates the differences between the scenarios. We believe that adding 27 million DALYs saved to each scenario is a rough approximation for the benefit of campaigns that does not lead to a substantial over- or under-estimate of the effects of predictability and front-loading.

Appendix D: Acronyms

ADIP	Accelerated Development and Introduction Plan
DALY	Disability Adjusted Life Year
DPT	Diphtheria Pertussis and Tetanus
EPI	Expanded Programme of Immunisation
GAVI	Global Alliance for Vaccines and Immunization
HepB	Hepatitis B
Hib	*Haemophilus influenzae* Type B
HMT	Her Majesty's Treasury
IPV	Inactivated poliovirus vaccine
IFF	International Finance Facility
IFFIm	International Finance Facility for Immunisation
IFFIm Co	IFFIm Company
IMF	International Monetary Fund
LIC	Low Income Country
MDG	Millennium Development Goal
NPV	Net Present Value
OPV	Oral Polio Vaccine
PPP	Purchasing Power Parity
UK	United Kingdom
UNICEF	United Nations Children's Fund
VF	Vaccine Fund
VPD	Vaccine Preventable Diseases
WHO	World Health Organization

Notes

[1] This analysis draws extensively on models developed by the Immunization, Vaccines and Biologicals Division of the World Health Organization, and by Chris Gingerich. We are most grateful to them for making these available to us, and for their extensive support to enable us to make effective use of them. In particular, we are grateful to Lara Wolfson, Michel Zaffran, Maureen Birmingham, Patrick Lydon and other staff of the WHO for their contributions. While this analysis would not have been possible without their support, any errors in this analysis are entirely our own.

[2] Gordon Brown said on 26 January 2005: "GAVI have, together with the UK, France and the Gates Foundation, developed a proposal to apply the principles of the IFF to the immunisation sector --- with donors making long term commitments that can be leveraged up via the international capital markets in order to frontload the funding available to tackle disease." See http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2005/press_09_05.cfm and http://www.iffim.com.

[3] *Vaccines are cost-effective: a summary of recent research*. GAVI Research Briefing. Available at: http://www.vaccinealliance.org/General_Information/Immunization_informa/Economic_Impact/vacc_cost.php See also *Investing in Health. The World Development Report 1993*. World Bank, Washington DC.

[4] See *International Finance Facility for Immunization (IFFIm): Main Proposals*, UK Mission to the United Nations. Downloaded from http://www.ukun.org/articles_show.asp?SarticleType=17&Article_ID=881

[5] Even better value for money could be achieved if spending could be front-loaded and predictable without resorting to private sector borrowing.

[6] The total increase comes to more than the sum of the parts because the effects cumulate, ie 1.11 x 1.10 = 1.221.

[7] As explained later in the document, the estimate of DALYs saved is likely to be biased downwards by the use of sub-regional, rather than national, estimates of the burden of disease. This means that the cost per DALY saved is biased upwards. This bias should affect all three scenarios broadly equally. The health benefits of future vaccinations are discounted to today at 3% per year.

[8] Excluding cost of polio stockpile at $189m in all three scenarios.

[9] See WHO Vaccines, Immunization and Biologicals Department *History of Vaccination* http://www.who.int/vaccines-diseases/history/history.shtml

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[51] People are assumed to die at a constant rate. This constant rate is equal to the inverse of the life expectancy.