Forecasting for Global Health:
New Money, New Products & New Markets

Background Paper for the Forecasting Working Group

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Contents

Executive Summary

The Challenge: Forecasting as an Essential Part of Improving Access to Medicines in the Developing World

Lack of accurate and credible information about the demand for essential health products costs lives. Gaps and weaknesses in demand forecasting result in a mismatch between supply and demand – which in turn leads to both unnecessarily high prices and supply shortages. Children don't get malaria medicines that will save their lives, pregnant mothers don't sleep under impregnated bed nets, and those living with AIDS miss their medicine cycles, jeopardizing their lives and contributing to the risk of viral drug resistance within their community.

Although it is only one step in the long and often complicated supply chain, demand forecasting represents a key point of decision-making for both buyers and suppliers. If demand forecasting isn't done well – given inherent uncertainties, particularly for newer markets – the rest of the supply chain cannot be efficiently mobilized to deliver treatment.

Demand forecasting serves four functions critical to the effective delivery of medicines and supplies:

1. Allowing manufacturers to *plan capacity for existing products*, ensuring sufficient supply to meet demand.

2. Providing manufacturers with *information about new market potential,* permitting them to efficiently allocate resources for developing, producing and commercializing new products.

3. Enabling health systems in developing countries to *build the capacity to deliver products,* matched to the scale and mix of products required.

4. Allowing donors to *efficiently allocate their resources* by ensuring optimal prices and adequate supplies of products.

Pharmaceutical companies and vaccine manufacturers are well aware of the political and economic dangers of poor forecasting. While these challenges exist in both developed and developing countries, historically higher profit margins in rich countries have allowed manufacturers to use responsive, more expensive supply chains and some excess inventory to buffer against market uncertainties.[1, 2] Developed markets are also characterized by relatively good information and market research, and by purchasers and suppliers with established relationships and balanced market power.

In developing countries, forecasting problems are more difficult to resolve because of both "unknowns" and "unknowables." Markets are nascent with limited and unreliable data, few tools exist to gather good market research, profit margins are much lower or, in some cases, non-existent; uptake rates are unknown and dependent on poor health care systems; and in donor funded markets, financing flows are unpredictable. These weaknesses are particularly difficult to overcome because markets are typically small and forecasting accuracy is essential for products with complicated storage requirements (e.g. cold chain required in distribution of vaccines) and short shelf lives.

At the same time, the costs of doing business in developing countries are also higher than in developed markets, due to multiple international and national approval processes, supply chain bottlenecks, and country specific packaging in multiple languages. These issues are complicated by the fact that 'true markets' – in which sovereign consumers determine the quantity of a given product they are willing to buy at a given price – do not exist in many low income countries. Public sector patients often do not pay for products, funding is typically provided by donors, and product prices are often set at cost; the rules governing typical commercial market dynamics don't apply in these situations, making supply and demand problems more difficult to

resolve.[3]

The sad consequence of these outcomes is that a child in Zambia must wait at least 3½ years longer than a child in the U.K. to get access to life-saving treatment in the public sector, **even when money is available**.[4]

Like poorly performing health systems, ineffective supply chains in developing countries represent chronic problems. Why has the dilemma now become acute? The most significant drivers are the infusion of substantial new resources for the treatment of diseases that affect the developing world, and the development of new drugs and vaccines to treat or prevent these diseases. This has shifted the global dialogue from a steady set of pleas for more money to an increasing awareness that the resources available must be used effectively and expeditiously to fulfill the promises made.

These new monies have created markets for products in developing countries that never existed in the past and provide an opportunity to address chronic problems. The new funds to be disbursed through the Global Fund to Fight AIDS, TB and Malaria (Global Fund) alone demonstrate how significantly the market for health products has grown: between 2001 and 2005, spending for products to treat these three diseases more than doubled, and is expected to double again from $600 million in 2005 to $1.1 billion in 2006.[5] This represents a major step change in global needs for products which requires significant new investment in capacity by manufacturers and countries. This dramatic increase has already overwhelmed stressed supply chains, to the point that Global Fund recipients currently experience 5-18 month lead times in product procurement alone. Some of this is caused by slow bureaucratic processes, but an equally important problem has been – and may continue to be – critical supply shortages across a range of products unless action is taken.

The case of malaria illustrates the problem acutely. Critical supply shortages have existed over the past 12 months for artemisinin-based combination therapies (ACTs), which replace older chloroquine therapies that are now ineffective in many regions due to resistance; and for long-lasting insecticide treated mosquito nets (LLINs) – both innovations that have the potential to treat and prevent millions of malaria cases.

In 2005, demand from Global Fund recipients alone for Coartem[6] (the most widely used World Health Organization (WHO) pre-qualified ACT) was initially expected to reach 50 million treatments.[7] A concerted effort by international agencies, funders and most importantly the manufacturer, Novartis, rapidly increased production to 30 million doses. However, real demand by the end of 2005 was only 14 million treatments, resulting in a situation of oversupply by the end of 2005 at a significant cost.

For LLINs the story is similar. The development of mosquito nets that come pre-treated with insecticide lasting 3-5 years (rather than requiring re-treatment every 6-12 months) is an innovation that could greatly enhance malaria prevention. However, until recently, manufacturers scaled up capacity slowly because of insufficient engagement between suppliers, international agencies who forecast patient needs, donors who fund those needs and countries who purchase products. In Ethiopia, these shortages, coupled with an ineffective supply chain, prevented the provision of protection and treatment against malaria during two rainy seasons, potentially leading to thousands of avoidable child deaths.

In both cases, credible, timely, and coordinated demand forecasting, in collaboration with all stakeholders, could have reduced short term shortages and subsequent oversupply while demonstrating the true market potential to new entrants increasing competition in the market. These examples also show that while financial resources for developing country diseases are growing, manufacturers remain hesitant to invest in producing and commercializing drugs that are primarily or exclusively for the developing world without credible demand forecasts.

This vicious cycle – poor data paired with new technologies and rapid scale up needs – hinders the development of a robust, competitive market. The lack of a robust market, in turn, leads to supply shortages

or unaffordable prices, and ultimately unnecessary sickness and death. The objective of the Forecasting Working Group is to identify opportunities to break this cycle. This paper sets the stage for the Working Group by posing key questions to consider and providing an overview of the health product supply chain, demand forecasting initiatives, and methodologies. This context will enable all Working Group participants to have a shared starting point for discussion.

The Opportunity: Forecasting Working Group to Identify Methodologies and Mechanisms to Address Demand Forecasting Challenges

Various organizations including the WHO, the new product development public-private partnerships, the Global Alliance for Vaccines Initiative (GAVI), the Clinton Foundation, the United Nations Population Fund (UNFPA), procurement agents and suppliers are involved in forecasting need and demand for specific drugs and products for particular countries.[8] However, demand forecasting at the global level remains largely neglected. In this context it is important to clarify the difference between needs forecasting and demand forecasting. Within international agencies, demand forecasting often really denotes "needs forecasting" – i.e. the number of people affected by a disease based on epidemiological data and the proportion of those requiring treatment – and is frequently used to advocate for international awareness of the disease. New efforts are underway to turn these projections into 'product needs forecasts' still with a focus on advocacy.[9] Funders use "demand forecasting" to mean "resource forecasting" to project requests for future financing, usually from the donor community.

Ensuring the appropriate availability of drugs at an optimal price, however, requires forecasting that has sufficient certainty around funding and timing of orders to allow suppliers to confidently invest in production capacity. Suppliers must pre-finance raw materials and intermediate products and (in cases requiring large scale-up) make capital investments for new production facilities, which can take at least three years to build and accredit. Simply projecting product needs is insufficient to encourage this type of investment. For our purposes, we will use the following definition of demand forecasting which goes beyond projecting needs, to defining expressed demand in the market (i.e. product needs for which there is purchasing power that will result in actual orders). This definition clearly links demand forecasting to supply planning.

> *Demand forecasting is the process of planning and determining which products will be purchased, where, when, and in what quantities.*[10]

In other industries, the current conditions call for forecasting methods that encourage dialogue among a diverse set of players through systematically gathering and sharing available information, creating scenarios independent of political pressure, and combining forecasts from various sources for greatest accuracy.[11, 12]

There are, in fact many who could provide valuable input to forecasting for health products, but no focused forum exists to bring these groups together. The Forecasting Working Group will serve as such a forum to bring together a broad range of global health stakeholders with experts from other industries and disciplines in order to generate critical thinking on the subject of forecasting and develop recommendations for a broad set of actors on ways to improve forecasting and better match supply to demand.

With this perspective, the charge of the Working Group over a 12 month period will be to address six key questions:

1. What are the underlying reasons that forecasting is not working in the current environment for existing and new essential health products?

2. What are the economic costs and health impacts of poor forecasting?

3. What defines 'good forecasting' that effectively matches supply and demand? What mechanisms have successfully addressed demand forecasting challenges in other sectors or geographies and in particular areas of global health? What lessons from these examples can be applied to a wide range of global health products?

4. What tools and methodologies in data collection, analysis and estimation could lead to more credible and accurate aggregate forecasts for health products?

5. What modifications or innovations in market incentives, risk-sharing, purchasing or funding mechanisms could improve demand forecasting and supply planning?

6. What is the cost/benefit of each potential forecasting innovation? How could innovations be prioritized and who should pay for these?

The focus of the Group's recommendations will be at the global level and on the development of aggregate forecasts. The target audience for the Group's work includes policy makers in developed and developing countries, multi- and bilateral donors, public-private partnerships involved in product development, nongovernmental organizations (NGOs), the WHO, and procurement agents such as the United Nations Children's Fund (UNICEF), among others. A key focus of the group will be on donor-funded markets, which present challenges distinct from those faced in privately funded markets in developing countries. However, the group will also consider privately funded markets, particularly as they impact donor-funded and public sector market dynamics and influence overall supply and demand for products.

This paper frames the Working Group's efforts and highlights important background information. It is based on interviews with a diverse group of stakeholders including pharmaceutical companies, international agencies, procurement agents, public-private partnerships, funders, and purchasers. It also draws on recent literature and data available in the public domain.

Sections I and II of the paper provide an overview of the issues, identifying the key problems and their importance given the changing healthcare landscape and examining demand forecasting within the larger context of the health care supply chain. Section III provides an overview of what we know about forecasting in general, including various methodologies that might be useful to consider. The paper ends by highlighting opportunities for innovation and activities that the Working Group may consider.

The Imperative to Do This Now

The interviews and other inquiries conducted in the preparation of this paper support the premise that in global markets there is clearly a 'public good' in understanding the aggregate demand for health products and being able to plan for this demand. There appears to be a broad consensus around three conclusions:

1. First, demand forecasting is an essential element of ensuring the adequate supply of existing and new health products in the developing world. Suppliers all cite this as their single greatest need to ensure adequate supplies of products. The need for credible forecasting is particularity urgent in new markets, including both markets for new products (e.g. ACTs for malaria, potential AIDS vaccine) as well as markets for existing products that have received significant infusions of new funds (e.g. ARVs for AIDS).

2. Second, attention on demand forecasting has historically centered on improving country-level data collection; little attention has been given to aggregate forecasts at the global level and the impact of accurate forecasting on ensuring sustainable markets for drugs and supplies. Understanding aggregate demand is necessary to stimulate investment in product development, scale up production, leverage the purchasing power of global funders, and use scarce resources more effectively.

3. Finally, better demand forecasting at the global level is necessary and urgent to improve the effectiveness of the substantial new monies devoted to development assistance for health. Significant sums of money are being invested by donors for purchasing products and developing new products. Efficiently matching demand and supply for these health products is critical to effectively using these resources.

I. Why Is This Important Now?

Demand forecasting is just one component of supply chain planning for drugs and products. Ineffective supply chains in developing countries represent a chronic problem. Despite investments by the World Bank, USAID, and other donors to strengthen in-country supply chains over the past 10 years,[13] problems persist and efforts to address them remain intermittent and often uncoordinated.

Why has the problem of demand forecasting become acute now? The most significant drivers are the infusion of substantial new monies for the treatment of diseases that affect the developing world, and the development of new drugs and vaccines to treat or prevent these diseases. This has shifted the global dialogue from a steady set of pleas for more money to an increasing awareness that the resources available must be used effectively and expeditiously to fulfill the promises made.

The increase in donor funding has created markets for existing products, encouraging new suppliers to enter developing country markets and encouraging manufacturers to invest in research and development (R&D) for medicines that may benefit developing countries. However, it has also highlighted our lack of knowledge about these markets, particularly:

1. The impact of more money and new aid instruments on supply chains

2. How growing numbers of manufacturers from developing countries will affect drug security, access, and supply planning

3. The incentives (sometimes perverse) created by mechanisms which often separate those who pay for products (e.g. donors) from those who are actually responsible for their purchase (e.g. recipients)

4. The many factors which influence the uptake of products, and countries' purchasing decisions

5. How prices affect demand in donor funded markets

Each of these is discussed in greater detail below.

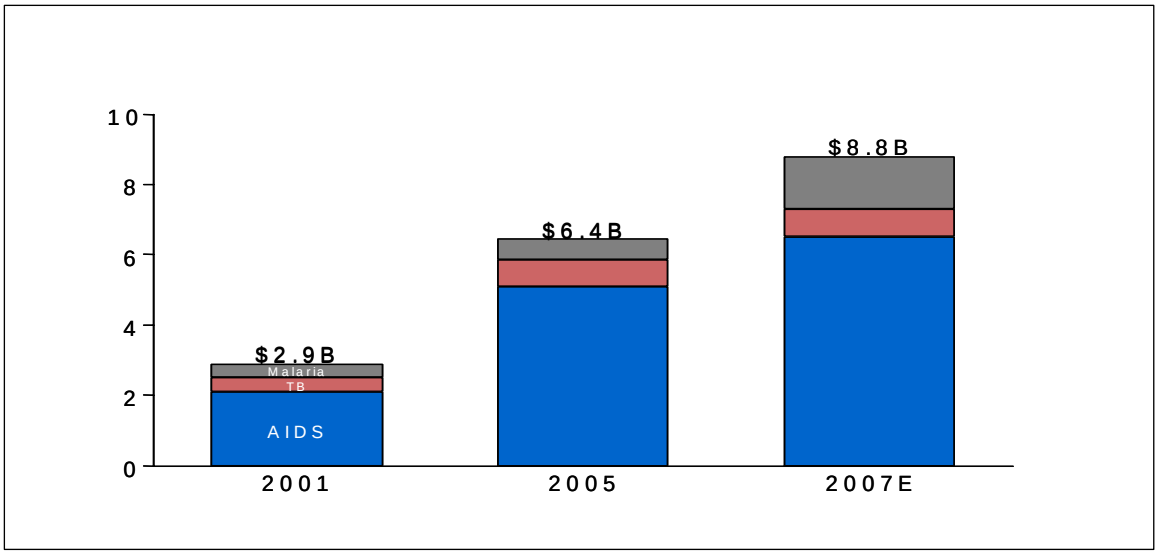
1. The Impact of Increased Funding on Supply Chains

The amount of donor funding for global health has increased substantially in the past five years, particularly for HIV/AIDS, tuberculosis, malaria, and vaccines. The U.S. alone has made a commitment in principle to spend $15 billion for HIV/AIDS through the President's Emergency Plan for AIDS Relief (PEPFAR) from 2003 to 2008. USAID has increased its funding to combat malaria from $22 million to $89 million between 1998 and 2005; and for tuberculosis to $408 million in 2004.[14] Globally, annual funding for AIDS, TB and malaria has more than doubled from 2001 to 2005; by 2007 the funding target is $15 billion for the three diseases, with $8.8 billion already committed by major donors.

For vaccines the situation is similar; in 2004 UNICEF alone purchased 2.8 billion doses of vaccines worth a total of $374 million, compared to only 969 million doses worth $55 million in 1990 – an almost 600% increase in spending.[15]

While financing gaps remain, the WHO, World Bank, and other international agencies all cite the bottlenecks in getting products and services delivered to those who need them as the biggest challenge to achieving the health Millennium Development Goals (MDGs).[16]

Figure 1: Funding for AIDS, TB and Malaria (2001-2007 estimates)



Sources: PEPFAR, Global Fund to Fight AIDS, TB and Malaria, World Bank

The increase in funds has had two significant impacts on supply chains. First, the increase in demand for products is a major step change for global capacity, not simply a gradual increase. Since its inception in 2000, the Global Alliance for Vaccines & Immunization (GAVI) has committed over $1 billion, and disbursed $533 million.[17] In the past three years, the Global Fund to Fight AIDS, TB and Malaria (Global Fund) has become the central financing arm in the fight against these three diseases, approving $8.9.billion in grants to 2010, and already disbursing $1.2 billion in 2005, with projected disbursements of $2.3 billion in 2006. Forty-nine percent of these monies are earmarked for the purchase of drugs and supplies.[18] This major increase in funding and subsequently in demand for products requires large investments by manufacturers to scale up production capacity. Within countries, it represents greatly expanded warehousing, storage, and logistics capabilities. Both require accurate forecasts to plan for and justify investments.

Second, new aid instruments, through which much of the new monies are being channeled, rely heavily on developing country supply chains that can deliver products quickly, efficiently, and at a large scale. These new performance-based funding instruments expect countries to show measurable results in a short period of time to justify continued disbursements. For example, Global Fund grants are initially approved for five years, but after the first two years of the grant cycle recipients must demonstrate good performance against targets to continue to receive funds. According to the Global Fund's estimates, the procurement process alone for medicines and supplies could take up to 18 months during its first round,[19] a figure consistent with experience from the World Bank.[20] Clearly, to meet the requirements of these new aid instruments, procurement mechanisms and supply chain processes must be greatly streamlined and strengthened, requiring investment in skilled staff and infrastructure.

2. Growing Markets Increase Complexity of Supply Chains

On a global scale, the number of actors in the supply chain continues to expand, creating more complexity in accurately forecasting and managing the supply of medical products. Currently, the market for newer products is characterized by numerous, small, disaggregated buyers, and a few internationally approved suppliers. On the purchaser side, large funders such as the Global Fund have chosen to disaggregate their purchasing power resulting in a plethora of relatively small orders; for example, although Global Fund commitments in total provide $1 billion for HIV/AIDS drugs, the average purchase order from a grantee is estimated at only $42,000.[21]

At the same time, the number of suppliers is also increasing. India and China, already significant players in the global pharmaceutical market, are growing. Recently, due to the fear that TRIPS[22] compliance will affect the Indian supply of generics to the developing world, some donors and international agencies are encouraging and funding the development of pharmaceutical manufacturing capacity in the Least Developed Countries (LDCs), which will not become TRIPS compliant until 2016.[23] Manufacturing of ARVs in the Democratic Republic of Congo is already underway and plans to expand manufacturing capacity to Angola and other African counties are under discussion.

Even as the number of suppliers is expanding, some experts suggest that recent changes in rich country markets may actually decrease the security of supplies to the developing world. Several Organization for Economic Cooperation and Development (OECD) countries have introduced initiatives to contain drug costs and expand markets for generics, increasing the attractiveness of rich country markets for developing country generic companies. This could make creating and manufacturing products for developing country markets relatively less attractive for both research-based and generic suppliers. For example, with the passage of new Medicare benefit proposals, generic manufacturers will be encouraged to enter the U.S. market;[24] another bill in the U.S. Congress calls for immediate removal of federal barriers to the importation of drugs from Canada, which would be extended to imports from other countries after two years.[25]

Fears about insecurity of the supply of essential drugs may be well founded. Even today, HIV/AIDS drugs are estimated to contribute only 10-15% of the profit margin of the two largest Indian generic manufacturers, Cipla and Ranbaxy, both of which already sell a wide range of generics to OECD countries. Recently, Ranbaxy received tentative approval from the Food and Drug Administration (FDA) for zidovudine (an AIDS drug), which allows the PEPFAR program to purchase its drugs overseas, and Aurobino Pharma, another Indian generics manufacturer, was granted full approval by the FDA for two formulations of zidovudine. This set the stage for these companies to sell to the profitable U.S. market when the GlaxoSmithKline product, Retrovir, came off patent in September 2005.[26]

These changes, and the growing potential for developing country manufacturers to participate in "first-world" markets, suggest that efforts must be made to encourage suppliers to stay in developing country markets. One way to do this is to create credible demand forecasting processes in collaboration with suppliers that quantify developing country market potential.

3. The Funder/Purchaser Split Diffuses Risks and Incentives

In developed countries, wholesalers and governments who purchase drugs also pay for them, and consequently bear the costs of poor forecasting. Both suppliers and purchasers share common bottom-line pressures to make sure that shortages don't occur and that costly excess inventory isn't wasted in warehouses. In developing country markets, risks and rewards are more diffuse. Suppliers are not able to easily pass on costs for excess supply to customers, but run a reputational risk for shortages.

On the purchaser side, the donor/purchaser split can blur incentives and lead to a situation somewhat analogous to the problem of moral hazard in insurance markets, where the user of services is protected from realizing the direct costs of his/her choices and may consume more services than actually needed. In the case of donor funded markets, typically the purchaser in-country bears a public health risk of undersupply, but is shielded from the financial risk and does not share in the rewards of buying at the optimal price. The same separation of funding and purchasing accountability protects countries from directly realizing the costs of wastage and holding excess inventory. In theory, donors bear the financial consequences of poor forecasting in paying higher prices for products and in waste. However, unless donors are also purchasers of products, they may not be concerned about, or even aware of, these costs.

4. Donor Funding Does Not Guarantee Uptake

Donor-funded markets are further distorted by the way in which different components of the supply chain are financed in developing countries. For example, although donors may provide drugs free to a country, the country bears the implementation responsibilities and switching costs from older therapies; both of these types of costs can be substantial in terms of re-training health personnel and creating new delivery mechanisms. GAVI, for example, has found that even when funding is available for new vaccine introduction and scale-up, countries are much slower to adopt these new products than traditional demand models would predict (Box 1). Once a country has switched to a new drug, it has less incentive to adopt a cheaper version if one becomes available because it is protected from the direct product costs by donor financing, but would have to pay again for the costs of switching.

Box 1: Uptake of Hepatitis B Vaccine

In its initial launch, GAVI made estimates of the amount of Hepatitis B vaccine that would be required based on epidemiological projections and the new monies that had become available. Several manufacturers, particularly in India, scaled up production or entered the market to accommodate these demands. However, uptake of the vaccine was much slower than predicted and consequently, the price dropped almost 80%, causing some developing country manufacturers to go out of business and making many companies nervous about future investment.

5. Demand Curve in Donor-Funded Markets Is Not Well Understood

Despite these market distortions, it is clear that purchasers in country are price sensitive because they have a responsibility to treat as many patients as possible with available funds, and also have a duty to ensure long term financial sustainability of programs. However, as a consequence of some of the issues mentioned above, the price elasticity of demand in donor funded markets is poorly understood across a broad range of products. Willingness to pay and substitution preferences apply at both the aggregate and individual levels and are influenced by a variety of factors including the presence of local suppliers, the implicit and explicit country co-payments that accompany donor funding of drugs and vaccines, patient cost sharing at the point of use, and donor commitments around sustainability and predictability of financing.

Impact of Inadequate Demand Forecasting: The Case of Malaria

The need for rapid scale-up puts pressure on buyers and manufacturers alike. On the supply side, critical supply shortages have existed over the past 12 months for artemisinin-based combination therapies (ACTs) and long-lasting insecticide treated mosquito nets (LLINs) – both innovations that have the potential to treat and prevent millions of malaria cases.

With its drug Coartem, Novartis became the initial commercial producer of ACTs, which replace older chloroquine therapies that are now ineffective in many regions due to resistance.[27] However, Novartis' production of ACTs was temporarily insufficient to meet the large increase in demand driven by a rapid country-level policy shift to ACTs, which had been anticipated by the international health agencies at a late stage, paired with significant influx of new financial resources from the Global Fund. In 2005, demand for Coartem from Global Fund recipients alone was initially expected to reach 50 million treatments, but in reality came in at only 14 million treatments. Total production capacity will yield 30 million treatments, creating an oversupply situation by the end of 2005.[28]

For LLINs the story is similar. The development of mosquito nets that come pre-treated with insecticide lasting 3-5 years (rather than requiring re-treatment every 6-12 months) is an innovation that could greatly enhance malaria prevention efforts. However, until recently manufacturers scaled up capacity slowly because of insufficient engagement between suppliers and international agencies who forecast patient needs, donors who fund those needs and countries who purchase products. Precipitated by critical shortages, a concerted effort of key international players including the Roll Back Malaria Partnership, WHO and the Global Fund was initiated,[29] and the two approved existing manufacturers agreed to increase production. New entrants are

also showing interest in investing in this market. Estimates of future funding and resulting demand have played an integral role in strengthening the interest of suppliers, but current forecasting efforts have been mostly ad hoc and rely on existing data and conditions, rather than accounting for the many factors that may affect future demand.

In both cases, better demand forecasting may not have prevented some shortages in the early stages of market development but could certainly have reduced them. Perhaps even more importantly, credible demand forecasts could have demonstrated the market potential to new entrants, increasing both supply and competition in the market.

Demand Forecasting in Major Donor-Funded Markets

The section below summarizes some of the key forecasting challenges for the large and growing donor-funded markets for vaccines, malaria, HIV/AIDS and tuberculosis. More detail on each of these markets can be found in the appendix.

While each area faces different forecasting challenges given the stage of its market and the complexity of product choices, several common themes emerge:

- Few formal mechanisms exist to create broadly accepted demand forecasts that take advantage of increased funding to encourage manufacturers to scale up supply. As a consequence, supply shortages are becoming increasingly common for existing products.

- There is no formal mechanism to use forecasting of funded demand to encourage new product development and new entrants into the production chain. Several public-private partnerships have been created for new product development, and an "advance market commitment" (AMC) for vaccines is being considered; however, these still rely on fragmented and frequently ad hoc forecasting processes to estimate long-term demand and the timing of this demand.

- There is a surprising lack of reliable information on the number of people affected by particular diseases in the developing world. Inconsistency in data collection, lack of adequate surveillance sites, and methodologies for data analysis which are not transparent, all contribute to uncertainty in underlying patient needs forecasts, and consequently, in determining demand for products. Improving these data is one of the aims of the Health Metrics Network, which is being funded by the Bill and Melinda Gates Foundation and will be housed at the WHO.

Key issues in each market are highlighted below.

1. *Vaccines:* Historically, the high development costs and low profitability of vaccines have resulted in few incentives for manufacturers to enter or remain in this market. By 2002, UNICEF, which purchases vaccines for 40% of the world's children, was buying from only two vaccine suppliers.[30] The creation of GAVI in 1998 dramatically changed the landscape by acting as a source of credible demand. New vaccines are now in development and funded demand has attracted new suppliers into the market.

   The consolidation of vaccine purchasers and suppliers in developing countries, and the standardization of products, makes demand forecasting relatively more straightforward in vaccine markets than in other areas. Despite this, as funding has become available for large-scale interventions, several forecasting challenges have been identified:

   - Unlike older vaccines, current products such as hepatitis B, pipeline products such as rotavirus vaccines, and potential products such as an AIDS vaccine, are likely to be more expensive and therefore more reliant on donor funding. Similarly, newer multivalent combinations are more

expense than smaller combinations. For example, compared to the traditional diphtheria-tetanus-whole cell pertussis (DTPw) combination vaccine at under $0.15 per dose, a single dose of the GAVI-funded pentavalent vaccine combining DTP-hepB-Hib costs approximately $3.60.[31] Concerns about affordability and sustainability of funding, as well as uncertainties about underlying epidemiological needs, makes it difficult to forecast the timing and extent of uptake.

- Although large procurement agents such as UNICEF forecast vaccine demand on a five-year rolling basis, they are not bound through their contracts to share the risk of excess supply costs with industry. Estimates may therefore be optimistic, partially driven by advocacy and country targets; in addition, methodologies to project demand are not transparent. Recognizing the critical role of accurate forecasting to encourage appropriate investment by industry, initiatives such as the Accelerated Development and Introduction Plans (ADIP) for pneumococcal and rotavirus vaccines are experimenting with various methodologies and incentive structures to better forecast demand.

- For new potential products such as a preventive AIDS vaccine, demand forecasting is very challenging due to high levels of uncertainty about:
    - vaccine characteristics (e.g. efficacy level, duration of protection and dosing regime);
    - vaccination strategies (e.g. targeting all adolescents, sex workers, IDUs etc.);
    - vaccination scenarios (e.g. the likely coverage/uptake rate); and
    - vaccine financing and procurement mechanisms.

  This uncertainty creates significant problems for demand forecasters, particularly when credible estimates are required to inform R&D incentives (such as an AMC) or to scale up manufacture and distribution channels.

2. *Malaria:* Markets for traditional treatments for malaria (insecticide-treated bed nets and chloroquine therapies) are well developed and have historically been funded through national programs. As mentioned earlier, many challenges remain in forecasting for malaria products for several reasons:

    - Although malaria has been endemic for hundreds of years in many parts of the world, there is still debate on the magnitude of the disease and estimates of people affected. The Roll Back Malaria estimates of between 300-500 million cases per year have been recently challenged by a University of Oxford study which shows the problem may be much larger than previously forecast, with up to 25% of total cases coming from the South East Asia and Western Pacific Regions.[32]

    - Technological innovations in prevention and therapy provide an opportunity for more effective treatment. These therapies, however, are much more expensive then traditional approaches and rely almost exclusively on donor funding. Because funded markets for these products are still new, there is a high level of uncertainty around speed of uptake, ongoing usage, timing of demand, and continued funding. These challenges will also apply to pediatric formulations and therapies still in the pipeline.

    - There has been no mechanism to develop aggregate forecasts for malaria products until very recently. The Malaria Medicines and Supply Service (MMSS) in the Roll Back Malaria Partnership has now taken on this role, and the Global Fund has also initiated meetings with manufacturers to apprise them of funded demand. As mentioned above, these efforts are ad hoc, not very accurate, and do not cover all critical products.

3. *HIV/AIDS:* Until recently, attention has focused on reducing the price of ARVs and scaling up funding for the purchase of these life-saving drugs. With the development of a generic triple-dose combination, strong price negotiation by the Clinton HIV/AIDS Initiative (CHAI) – from $15,000 per person/annum in rich countries to now $140 per person/annum for low-income countries – and large increases in

funding, these concerns are starting to be addressed. The three main forecasting challenges facing HIV/AIDS today are:

- The complexity of treatment and sheer number of products required for a comprehensive AIDS program is staggering. More than 200 different products are required to implement a program, including condoms, diagnostics, first and second line ARVs and consumable laboratory supplies. As an example, implementing a voluntary counseling and treatment (VCT) program in Tanzania and reaching the Government's target of 400,000 people on treatment requires testing and counseling of 20 million new individuals.[33] For ARV treatment alone, there are multiple regimens from which to choose and many product options, making forecasting extremely challenging.

- Although sufficient manufacturing capability exists for the final formulation of ARVs, supply for APIs (active pharmaceutical ingredients) is more limited. Shortages are projected for several APIs in the coming 18 months.

- No formal mechanism exists to develop aggregate demand forecasts for the multiple products required. The best forecasts that exist today for first line ARVs are done by CHAI (see Box 2) and may become the basis for more widely accepted forecasts. No aggregate forecasts exist for second line drugs and the wide range of diagnostics and consumables.

4. *Tuberculosis (TB):* Of the three diseases above, TB probably has the most well developed forecasts of underlying epidemiology and number of treatments required, at least for those on the WHO recommended Directly Observed Treatment Short Course program (DOTS). Two reasons for the success of TB forecasting are the early standardization of first line drugs by the Stop TB Partnership and the development of pooled purchasing of DOTS treatment through the Global Drug Facility (GDF). Also, unlike HIV/AIDS, TB programs are primarily funded through national resources and so the market for TB drugs is relatively more sustainable. The challenges facing TB forecasting now are:

   - Supply shortages and higher prices for raw materials, which are provided by only two main suppliers, has become a problem. Suppliers have not been able to keep up with rapidly increasing demand created by new funding.

   - The onset of multiple drug resistant TB (MDR-TB) will require new and more expensive drugs and greater engagement of all key stakeholders to ensure adequate supply. These drugs rely more heavily on donor funding, and the main supplier, Eli Lilly, is exiting the market. With WHO predicting shortages of these drugs in the coming months, international efforts are underway to attract new manufacturers into this market.

   - While GDF projects DOTS demand for its customers, no formal mechanism exists to forecast aggregate demand for all TB products.

Conclusion

The issues outlined above clearly present an imperative to address the challenges of demand forecasting in the context of strengthening global supply chains. Unless more effective and collaborative forecasting mechanisms are created that bring together industry, purchasers, funders and technical agencies, the security of pharmaceutical supplies to the developing world may be increasingly endangered.

II. The Current Process: Overview of Supply Chains in Low Income Countries

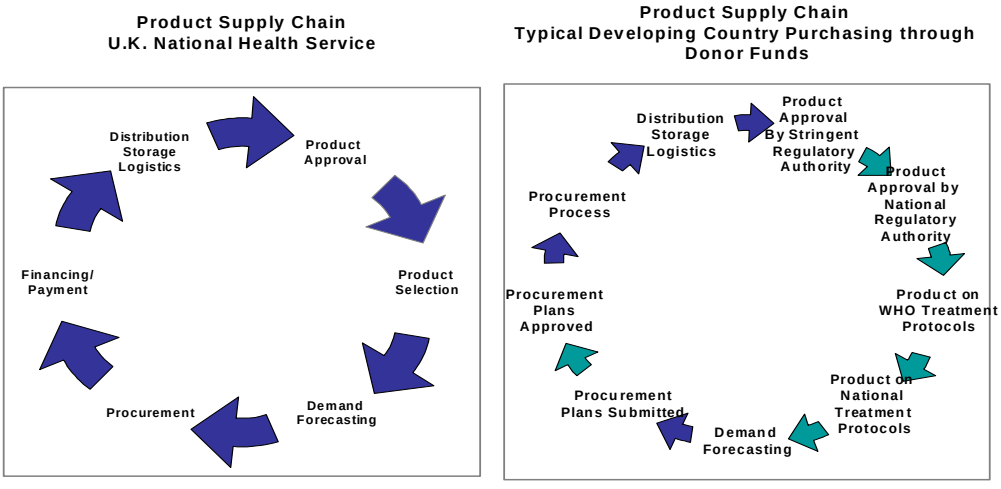
Demand forecasting is just one element in the entire supply chain for health products and it is worthwhile to look at this chain in greater detail to understand its interdependencies. Supply chains in health care are some of the most complex of any industry. Unlike many other global commodity chains, they must cope with fluctuating demand from changes in patients needs (including tolerance, resistance and unexpected outbreaks), short product life spans, innovative products with uncertain uptake patterns and demand, and susceptibility to disruptions from economic, political and regulatory changes in developing countries, which are often suppliers of raw materials and intermediary products.[34] Manufacturers and purchasers must finely balance efficiency with availability because shortages cost lives and come with significant political and economic consequences.

While these challenges exist in both developed and developing countries, historically, higher profit margins in rich countries have allowed manufacturers to use responsive, more expensive supply chains and some excess inventory to buffer against market uncertainties. Developed markets are also characterized by relatively good information and market research, and by purchasers and suppliers with established relationships and balanced market power.[35] For example, the U.S. pharmaceutical market (the largest in the world, accounting for 44% of all sales in 2003) has three wholesalers who cover 90% of the wholesale market.[36] Wholesalers are the major private sector customers of manufacturers, spending $212 billion in 2004.[37]

Developing country markets are nascent and much more complex. Data are limited and unreliable, few tools exist to gather good market research, and profit margins are much lower or, in some cases, non-existent. At the same time, disaggregated and small purchasers, and multiple layers of international and national decision makers, make the process more uncertain and more expensive for manufacturers.

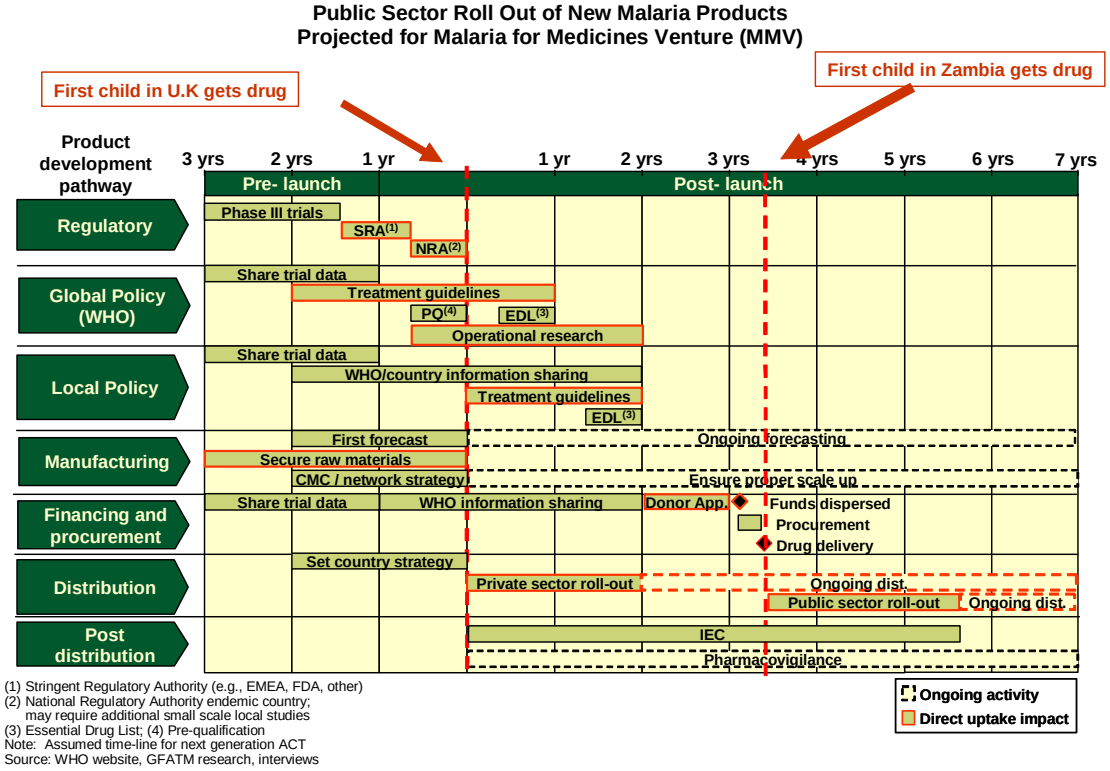
Figure 2 presents a stylized representation of the differences in the pharmaceutical supply chain in a developed market, the National Health Service (NHS) in the U.K, and a typical low- income country purchasing with donor financing.

Figure 2



The sad consequence of these differences is that a child in Zambia, for example, must wait at least 3½ years longer than a child in the U.K. to get access to a life-saving treatment in the public sector, even when money is available (Figure 3).

Figure 3



Source: Boston Consulting Group for Medicines for Malaria Venture

What causes these differences at each step of the supply chain?

1. Product Approval:

The large and lucrative NHS market (GBP 8.1 billion, growing at an annual rate of 10.8%)[38] makes it attractive for manufacturers to have their products registered for use in the U.K. If the drug has been manufactured outside of the U.K. by a PIC/S approved regulatory authority,[39] sharing of standards and dossiers between regulatory agencies make the approval process straightforward through the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA).

In contrast: If the developing country has a small market, the manufacturer may not have registered its drugs for approval by the national regulatory authority in the country. Unlike PIC/S approved authorities, requirements for dossiers are not consistent or shared among all countries. This makes the approval process for a supplier much longer, more complex and more expensive. Even if the drug has been approved for national use, most donors require approval from a PIC/S registered regulatory body or the WHO.[40] Once a supplier has requested country approval, the process can take an additional 6-12 months.[41]This can mean that even if multiple suppliers exist globally, many countries have access to only a single supplier. Some manufacturers cite these regulatory barriers as the single greatest hurdle to wider access to drugs in low income countries.

2. Product Selection:

In the NHS, after the manufacturer obtains approval of its drug from the MHRA doctors are free to prescribe it without further authorization from an NHS body or purchasing agency. There is no "white list" of approved drugs that can be ordered.[42] This is changing though with the development of treatment

guidelines by the National Institute of Clinical Excellence (NICE), and by regional technology assessment agencies; while these guidelines are not mandatory, they are increasingly being monitored by oversight bodies and considered in funding decisions.

In contrast: Donors generally approve purchase of drugs that follow internationally recognized treatment guidelines (usually developed by the WHO). These guidelines are created through processes which bring together international experts in "informal consultations" on an ad hoc basis.[43] Experts examine clinical evidence on the usefulness of the drug based on trials in developing countries, which are often not funded by manufacturers, prolonging the time needed to prove the drug's effectiveness on the ground. At the country level, national treatment protocols must be revised before the drug can be purchased with public monies, a process that can take 6-12 months. Separately, most developing countries have essential drugs lists (EDL) based on the WHO EDL and require that drugs procured by public funds are on these lists.[44] The WHO EDL is updated every two years in a process distinct from that used to create treatment guidelines. Changes in treatment protocols and prequalification can have a profound effect on the demand for branded versus generic drugs, prescribing patterns and overall drug costs.

3. Demand Forecasting:

In the NHS, national demand forecasting is done through a specialized technical agency outside of the NHS called the Purchasing and Supply Agency (PASA). PASA works with suppliers to forecast demand and establishes long term framework contracts through which NHS hospital trusts procure drugs and supplies.

In contrast: National and local demand forecasting systems in developing countries are often weak or non-existent. Although donors typically require procurement plans specifying which drugs a country will order and their purchasing timeframe, the quality of these plans varies. The dearth of good epidemiological data and consumption information, lack of trained personnel, and political pressures to achieve targets add high levels of uncertainty to these plans. In recent months, due to supply shortages and recognition of the importance of demand forecasting, various departments in the WHO have started to create aggregate needs and demand estimates for particular drugs; for example, the Roll Back Malaria initiative is beginning demand forecasting for new malaria drugs and the WHO AIDS Medicines and Devices Service (AMDS) is starting work on forecasts for first line ARVS. In addition, the Clinton HIV/AIDS Initiative already creates demand forecasts for ARVs to negotiate price agreements with suppliers (Box 2).

Procurement agents such as UNICEF and the GDF may also forecast demand for their customers. However, their planning horizons are often very short and procurement agents may not be able to provide 12-month rolling forecasts to manufacturers. In addition, the bidding process between agents and countries may result in double counting of demand, for example when multiple agents place orders based on unconfirmed bids. Government tendering processes can complicate these problems.

Box 2: Forecasting for ARVs

To negotiate prices with suppliers and active pharmaceutical ingredient (API) manufacturers, the Clinton Foundation HIV/AIDS Initiative (CHAI) recognized that it would need credible aggregate forecasts. Their process uses a bottom up approach of asking countries to produce forecasts for ARV needs. CHAI staff are located in 18 countries, where they work with governments to refine the national forecasts. This data is aggregated and assumptions and adjustments made for specific regimens for each country, treatment failure rates, and adult/pediatric needs. The forecasts are further adjusted for the likelihood that the country will achieve the target, creating low, medium and high scenarios. Forecasts are adjusted quarterly. Detail is provided for 42 countries, which represent 85% of ARV needs; the remaining 15% is extrapolated. Like the PAHO Revolving Fund (Box 3), CHAI works with countries to anticipate changes in treatment protocols and improve the functioning of the entire supply chain. In countries where CHAI has staff on the ground, forecasting is embedded into the broad technical support that CHAI provides to the country's national AIDS program.

4. Procurement:

For drugs prescribed in NHS hospitals, PASA negotiates contracts and prices with suppliers; NHS hospitals order independently, based on these rolling long term (6 year) agreements. PASA uses sophisticated electronic analytical tools to obtain the optimal price to encourage competitiveness and ensure drug availability.

In contrast: Most procurement in developing countries is conducted through rigid, paper-based competitive tender processes. Long term agreements sometimes exist, but typically with terms that yield neither significant pricing benefit to buyers nor increased certainty for suppliers. The bidding process itself can take from 6-9 months, and negotiators are often civil servants with limited training in contracting. Products can be available more quickly if international procurement agents are used, but agents usually negotiate only one-year agreements with suppliers and charge countries high fees (often 3% - 16% of product value).[45]

5. Financing and Payment:

In the NHS, once the hospital orders the drug, payments can generally be handled electronically. Financing is based on pre-established budgets. A new case rate payment system is being introduced for hospitals which may impact the prescribing patterns of physicians, but is unlikely to affect the electronic payment process for drugs.

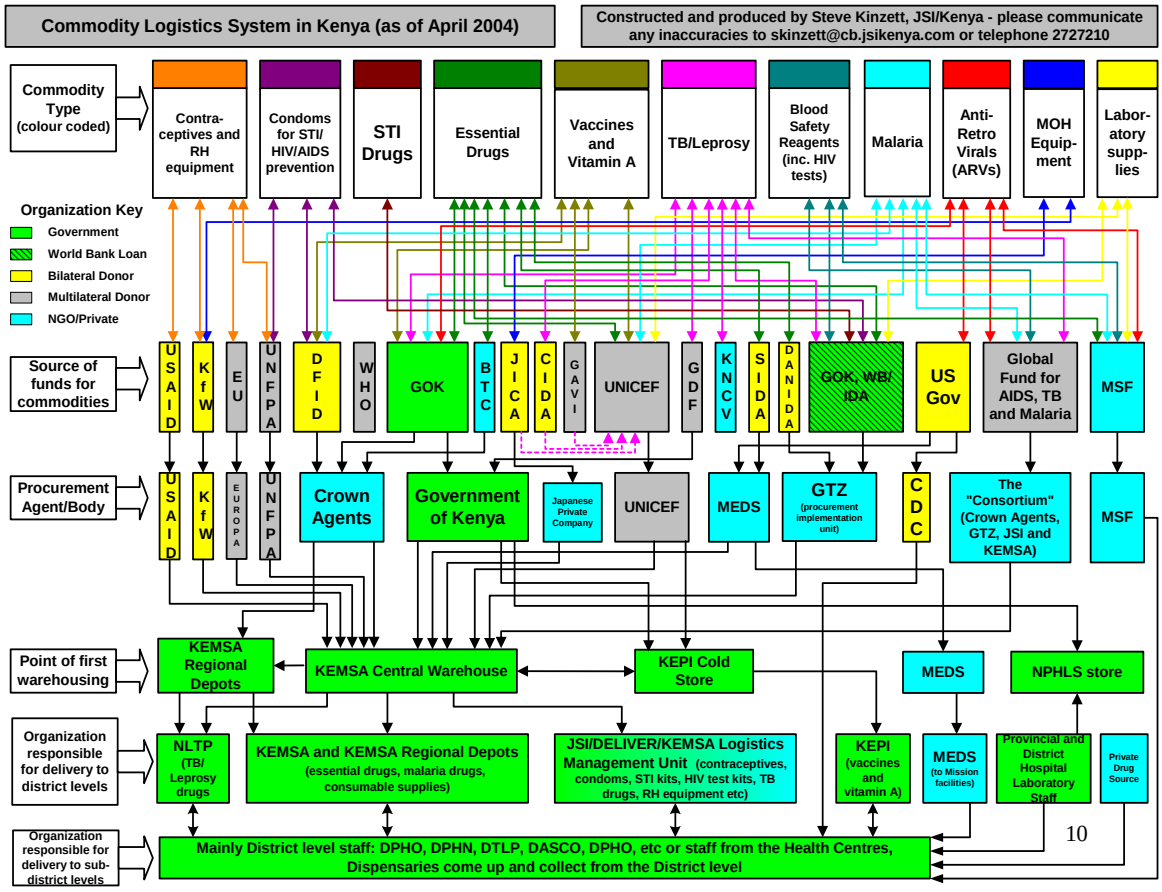
In contrast: While some donors undertake pooled procurement (e.g. the GAVI Fund), arrangements where products are purchased directly by countries are more common (e.g. the World Bank, most Global Fund grants). To release funds from a donor to a country for purchasing products requires multiple checks. Once funds are released, bureaucratic processes in-country, involving several ministries and layers of approval, can further delay financing approval, and consequently the ordering of necessary drugs and supplies. Even once drugs are received, uncertainties around costs for taxes, duties and customs costs can create delays. Insufficient planning for these items can mean that products can be held up in customs for months awaiting release of funds. Many procurement agents and companies also require partial pre-payment on orders, which may be difficult with current donor processes.

6. Distribution, Storage and Logistics:

In the NHS, distribution and logistics are handled either though an arms length body called the NHS Logistics Authority or directly through the supplier. The Logistics Authority runs warehousing facilities and keeps inventory for rapid distribution to hospitals.

In contrast: Difficulties in transportation, storage capability and logistics expertise make this a very cumbersome process in many developing countries as shown in Figure 4, which depicts the complex commodity logistics system in Kenya. Much has been written on in-country logistics issues and several donors are investing in strengthening distribution capacity.[46, 47] A study in Ghana estimates that the direct costs of the logistics system for drugs ordered through the Ministry of Health (MOH) is 13% of its total MOH budget; an astonishing 73% of this is for storage and warehousing.[48] Typically, donors do not fund the ongoing expenses of these functions.

Figure 4



Source: Steve Kinzett, JSI/Deliver Kenya

Conclusion

As shown above, developing country supply chains involve more players and are more ad hoc and less transparent than those in developed markets. At every level of the supply chain, there are potential bottlenecks that can cause delays in ordering and uncertainty in forecasting. Although the components of the supply chain are linked, the critical early role of forecasting affects all downstream processes such as the amount of money requested from funders, quantity of drugs ordered, time of receipt, storage method and capacity, and planning for transportation and distribution. Crucially, demand forecasting also affects upstream processes of development and production: without credible forecasts, suppliers cannot invest in manufacturing capacity and new suppliers will not enter the market.

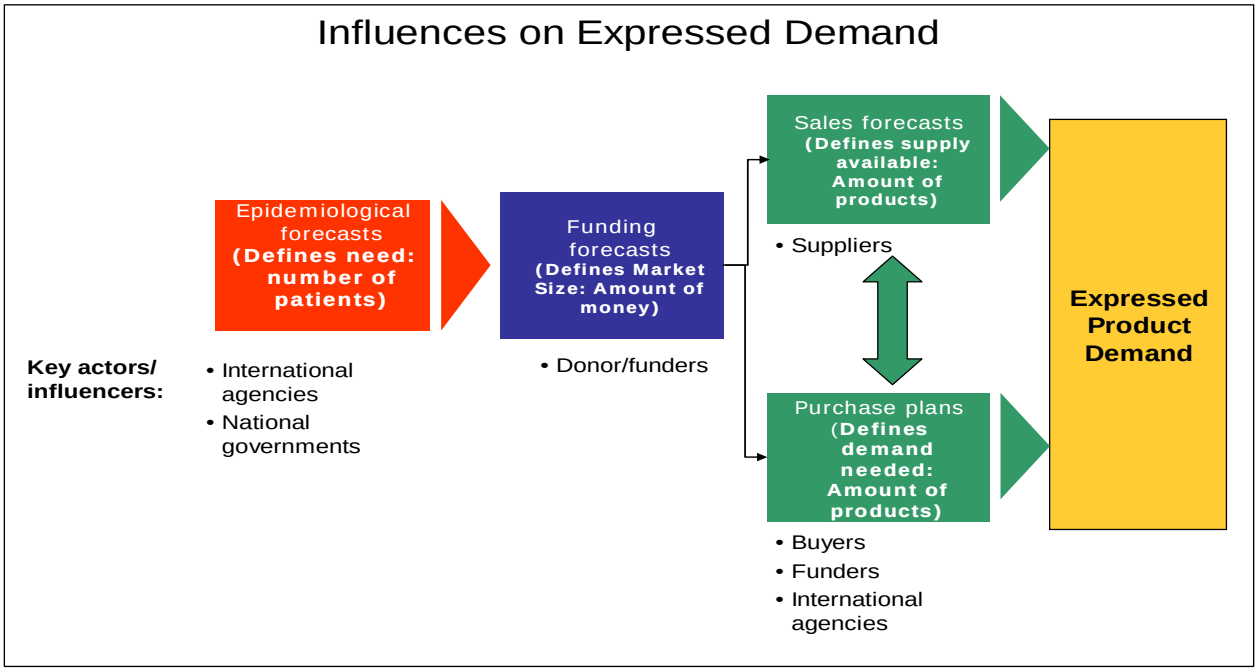
III. Demand Forecasting: An Overview

1. What Are We Forecasting?

The classic economics definition of 'demand' is fairly straightforward – it states that from the perspective of sovereign consumers, demand defines the quantity of a given product they are willing to buy at a given price. However, the term "demand forecasting" as used by various actors in the health supply chain does not often conform to this definition but reflects instead the particular forecasting needs of the player. Within international agencies, demand forecasting often really means "needs forecasting" – e.g. the number of people affected by a disease based on epidemiological data and the proportion of those requiring treatment – and is frequently used to advocate for international awareness of the disease. Funders use "demand forecasting" to mean "resource forecasting" to project needs for future financing, usually from the donor community. Purchasers or procurement agents define demand forecasting as short term supply needs based on annual budgets, i.e. the volumes and products they can commit to buy in negotiations with suppliers, driven by the orders they expect to receive. For countries, demand forecasts can range from short term ordering needs to the achievement of ambitious government targets. Finally, suppliers use the term demand forecasting to determine resource requirements in planning for new products, or in the case of existing products, to guide their investments in production capacity and raw materials.[49]

Each type of forecasting requires different levels of detail and certainty and is based on different units of measurement. At the most aggregate level are epidemiological forecasts of the number of people affected with a disease; at the most detailed are local forecasts on procurement needs taking into account distribution and warehousing capacities, logistics concerns and uptake of drugs at the individual facility level (see Figure 5). These forecasts have different cycles that rarely match one another; for example, Coartem production requires a 14-month lead time that does not accommodate short-term ordering forecasts in countries.

Figure 5



Ensuring the appropriate availability of drugs at an optimal price requires demand forecasting that has sufficient certainty around funding and timing of orders to allow suppliers to confidently invest in production capacity. Suppliers must pre-finance raw materials and intermediate products and, in cases requiring rapid

scale-up, make capital investments for new production facilities. Simply projecting product needs is insufficient to encourage this type of investment. For our purposes, we will use the following as a working definition of demand forecasting, which goes beyond the forecasting of need and emphasizes expressed demand in the market (i.e. product needs for which there is purchasing power), clearly linking demand forecasting to supply planning:

> *Demand forecasting is the process of planning and determining which products will be purchased, where, when, and in what quantities.*[50]

A couple of points are worth noting: First, forecasts are not plans or targets. Plans tell us how the future should look or how we would want it to look, while targets are goals used to motivate performance.[51] Forecasts tell us how the future *will most likely* look based on the best data and estimates available.

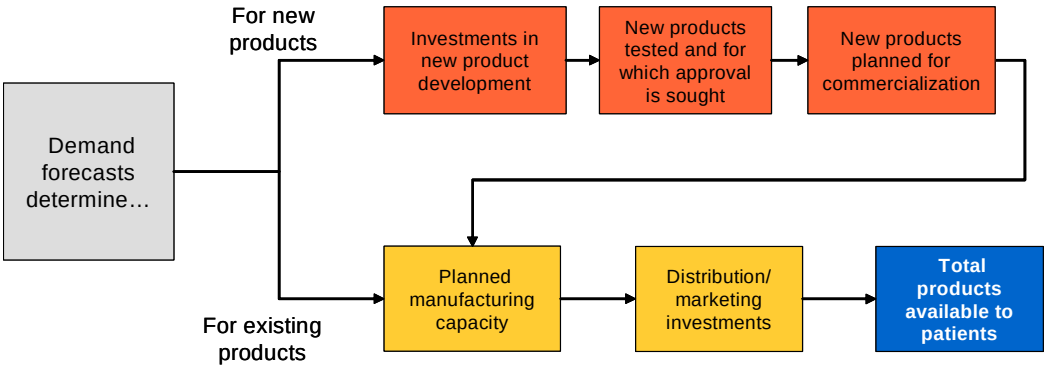
Second, uncertainty is inherent in forecasting. There is no need to forecast events where the outcome is certain or it can be completely controlled.[52] Though more quantitative data definitely improves the quality of forecasts, the costs of additional data collection must be weighed against their benefits.

2. Why Are We Forecasting?

The benefits of accurate forecasting are evident: improved customer service, greater market efficiency resulting from better production planning and lower inventory, adequate supply to customers, and early recognition and supply of future customer needs. Accurate forecasting can also be used as the basis for more robust incentives mechanisms (e.g. AMCs) to promote R&D into medicines to treat diseases of the developing world.

The risks of poor forecasting are equally evident: an inefficient market with higher prices and wasted capacity, supply shortages of current drugs, insufficient development of drugs for future needs, and inadequate investment in manufacturing capacity. As mentioned above, the critical position of demand forecasting in the supply chain also affects all the downstream processes that are particularly difficult in resource constrained environments. For example, if countries underestimate demand, drugs can wait in freight areas due to inadequate storage and logistics capacity; conversely, over-estimates can cause drugs to sit in warehouses past their expiration dates, wasting large amounts of scarce funds (Figure 6).

Figure 6: The Critical Role of Demand Forecasting



Since demand forecasting is clearly linked to supply planning, it is worth highlighting the key factors in pharmaceutical supply chains that make accurate forecasting challenging in any market.[53] In combination, these factors make it difficult to quickly adjust production capacity and accommodate large fluctuations in demand.

- The life cycle of a drug is influenced by the long and complex research and development (R&D) cycle, which is characterized by technical barriers of bio-technology, patient resistance and sensitivity. This often requires forecasting horizons of 10 years or more in a volatile environment to produce new products. This is especially true for vaccine preparations.

- Manufacturing for many products is characterized by long lead times for active ingredients that often depend on a limited number of global suppliers and are subject to economic and political disruptions. The process of production from raw materials to finished product takes an average of 9 months, and building and accrediting manufacturing facilities takes at least 3 years.

- The industry is highly regulated and regulators are increasingly vigilant about issues of patient safety and dumping of low priced products. This increases uncertainty that drug development costs can be recouped, even after drugs are brought to market. In some countries, such as the U.S., manufacturers are prevented from creating excess inventory and can only supply to meet demand forecasts.

- Historically, high margins and patent protection have allowed inefficiency in pharmaceutical supply chain processes. Consequently, forecasting between manufacturers and their suppliers is fragmented; the industry lags behind retailing, for example, in developing collaborative supply chains that can more effectively adjust to changes in demand. Cost containment efforts in developed markets are eroding supplier margins and encouraging more collaborative supply chains, but these changes are in the early stages.

- Sales and marketing management depends on the purchase and distribution of the product by various intermediaries, not the ultimate consumer, which means that the drug must be accepted as the preferred treatment in international and national treatment guidelines and essential drug lists. Doctors must also learn about the drug and agree to prescribe it, creating uncertainty in product uptake and its timing.

- Finally, for many R&D companies, developing countries do not represent true 'markets' because prices in some of the lower income countries are set to recover costs, rather than to generate a profit. In these cases, the sales objective is to make the drug available, not necessarily to promote drug sales and make profits. At the same time, the costs of doing business in developing countries are higher than in developed markets due to supply chain complexities, country-specific packaging in multiple languages, and uncertainty of funding.

The pharmaceutical industry uses numerous methods and electronic tools to address these forecasting challenges. These applications work best for existing drugs and in developed markets with good data and assured funding, where both purchasers and suppliers have complementary skills and information.

3. How Are We Forecasting?

Sophisticated forecasting methodologies exist, but the methods most common in health care are fairly straightforward, relying on direct human judgments with implicit rather than explicit assumptions and limited quantitative data. The two most commonly used methods are:[54]

- ***Consumption method:*** Uses historical data of past consumption to predict future requirements. This is obviously the most reliable method when good consumption data are available, for existing products, and for products where use patterns are well established.

- ***Morbidity method:*** Relies on underlying epidemiological information to estimate disease burden. This information is then combined with treatment guidelines to estimate the number of specific treatments

needed. In cases where multiple drugs may be used, estimates consider clinicians' expected prescription patterns and timing of uptake. The morbidity method is often used in developing country markets because of poor consumption data. However it suffers from sometimes significant uncertainties about underlying epidemiology, actual treatment regimens that will be recommended and the frequency with which these will change. At the country level, insufficient data are available on local absorption patterns, uptake, and capacity.

The purpose of forecasting is both to increase the accuracy of demand estimates and to asses the risk or uncertainty associated with various options or outcomes. There are several existing forecasting techniques that are improvements over these commonly used methods, including structured methods of using qualitative judgments, and combining qualitative and quantitative inputs. These require special technical skills in forecasting, however, and may be difficult to implement at local levels. While it is beyond the scope of this paper to present an exhaustive description of forecasting methodologies, the section below highlights a few techniques used in other industries that could be considered in health care markets. Armstrong and Green provide an excellent summary of demand forecasting methods in "Demand Forecasting: Evidence Based Methods."[55]

The first critical step of forecasting is to clearly define the forecasting problem so that all stakeholders understand the scope of the forecast and its ultimate use.[56] Only then can an appropriate methodology be selected to fit the forecasting environment. Figure 7 presents a decision tree that narrows the range of possible forecasting methods based on their suitability in various environments. In the case of a typical developing country forecasting demand for ARVs, for example, the decision tree points to methods that integrate human judgments with quantitative data in structured ways.

The degree to which the appropriate method for a particular situation relies on qualitative input from human judges, structured combinations of quantitative and qualitative information, or statistical techniques will vary based on the product's life-stage and market conditions.

- *Methods based on judgment, or qualitative forecasts,* are most useful when special events or discontinuities exist in the environment and when quantitative data are very limited. However, human judgments are subject to various errors which may be compounded when groups meet to agree on forecasts by dynamics such as 'groupthink' and the presence of dominating individuals or differences in power relationships. Several methods capture qualitative input more systematically than simple use of experts, including Delphi techniques, prediction markets, structured analogies, game theory, judgmental decomposition, judgmental bootstrapping, expert systems, simulated interaction, intentions and expectations surveys, and conjoint analysis. These require special training and rigorous application.[57]

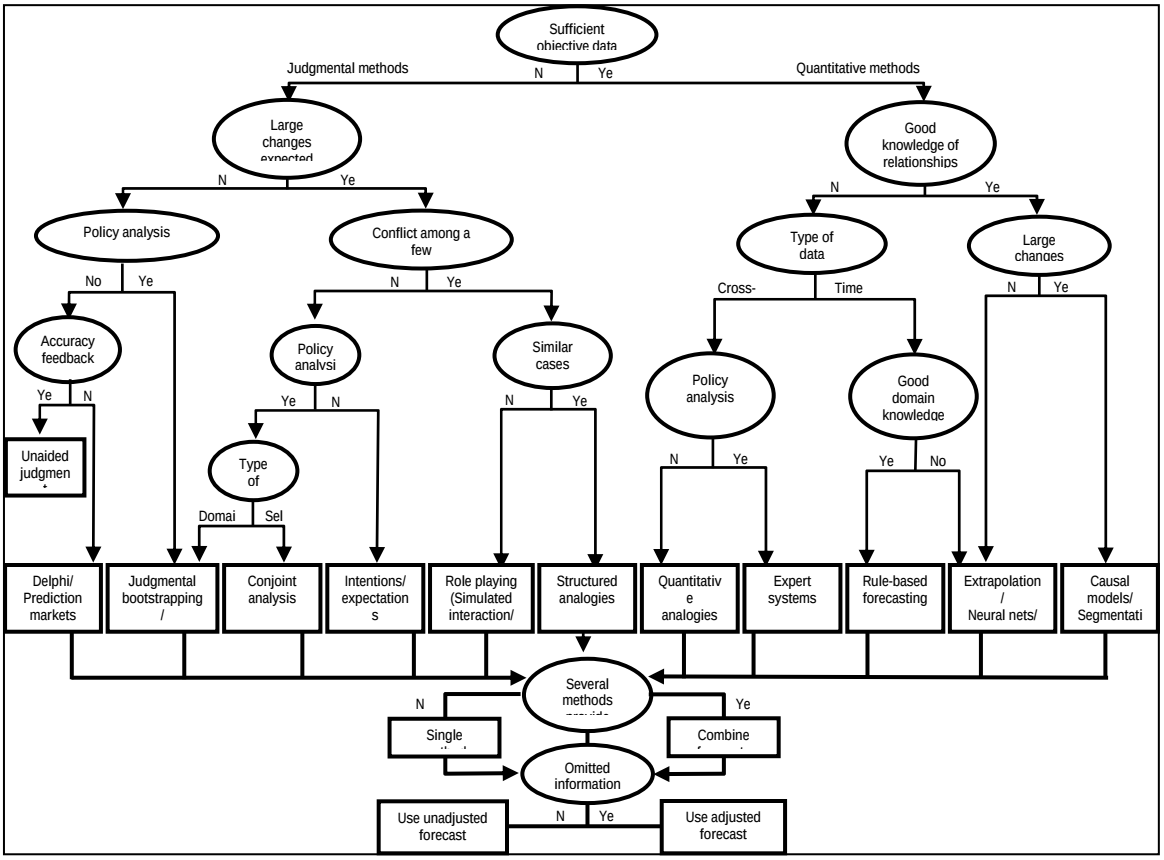
- As more data become available, *qualitative and quantitative information can be integrated* as long as it is done appropriately and systematically to avoid adding greater inaccuracy to forecasts. *Voluntary integration*[58] methods allow the human forecaster to adjust statistical forecasts based on explicit assumptions and can improve accuracy when the forecaster has specific contextual information or can affect the forecast (e.g. change purchasing decisions)[59] and when forecasters do not have pre-determined or political agendas for the final forecast.[60] 'Direct judgment,' whereby judges modify forecasts based on their personal knowledge, is the most frequently used method of incorporating qualitative input into forecasts, but is seriously flawed due to the variety of simplifying strategies that judges employ when assessing data, including a tendency to over-value the most recent data, underestimate the growth or decline in time-series data, see patterns in randomness, and inconsistently assign relationships between variables based on personal biases.[61] A variety of *mechanical integration* methods also exist which use statistical tools to integrate qualitative and quantitative judgments.[62]

- *Combining forecasts from diverse methods* is often done in business applications and can be useful when there are high levels of uncertainty or when it is unclear which methodology will produce the best results.

Combining works best if forecast errors in each method are negatively correlated and will cancel each other out, but this is difficult to achieve in practice.[63]

- As comparable time-series information becomes available and the market stabilizes, *statistical methods* are preferable for forecasting.[64] These include extrapolation, quantitative analogies, rule-based forecasting, neural networks, data mining, causal models, and segmentation. Integrating human judgments for special events or circumstances into these methods will still be appropriate.

Figure 7: Selection Tree for Forecasting Methods



Source: Armstrong J. Scott. Selection Tree for Forecasting. www.forecastingprinciples.com

Conclusion

New markets in developing countries with poor information present challenges for demand forecasters. However, as shown above, the field of forecasting is well developed and there are various techniques that can be applied in data-poor environments to increase both the accuracy and credibility of forecasts.

IV. The Opportunity: Information and Market Innovations to Improve Forecasting

While the substantial increases in aid and new aid instruments have stressed and highlighted the urgency of problems in demand forecasting, they also provide the opportunity, resources and mechanisms to create new global and national solutions.

This section highlights several ideas emerging from the interview process that address the key policy questions to be tackled by the Working Group. The examples shown are not recommendations, nor do they constitute an exhaustive list; they are intended instead to stimulate thinking around potential solutions that may be further explored by the Working Group. The discussion is grouped around six policy questions:

1. What are the underlying reasons that forecasting is not working in the current environment for existing and new essential health products?

2. What are the economic costs and health impacts of poor forecasting?

3. What defines 'good forecasting' that effectively matches supply and demand? What mechanisms have successfully addressed demand forecasting challenges in other sectors or geographies and in particular areas of global health? What lessons from these examples can be applied to a wide range of global health products?

4. What tools and methodologies in data collection, analysis and estimation could lead to more credible and accurate aggregate forecasts for health products?

5. What modifications or innovations in market incentives, risk-sharing, purchasing or funding mechanisms, could improve demand forecasting and supply planning?

6. What is the cost/benefit of each potential forecasting innovation? How could innovations be prioritized and who should pay for these?

1. Why Isn't Demand Forecasting Working in the Current Environment?

This paper identifies a number of factors which contribute to problems with demand forecasting in the present environment. These factors are diverse and far reaching, including: the major step change in the volume and types of drugs required because of substantial new monies, insufficient data capture locally and internationally, inadequate collaboration among critical players, complex supply chains, lack of institutional and planning mechanisms to prepare for global drug supplies, poor skills in forecasting at both international and national levels, disaggregated purchasing processes, new market entrants, and market distortions unique to donor markets. Some of these may be symptoms of the problem or contributing factors, while others are so fundamental that they must be solved to ensure drug security to the developing world. The Working Group may commission work to better understand these problems and others, and identify priorities for policy attention.

2. Economic and Health Impact of Poor Forecasting

Supply shortages impact public health and can cost lives and livelihoods. For suppliers, shortages result in lost sales and come with political consequences. Conversely, excess supply is costly to maintain and results in high levels of wastage for products with short shelf lives. As the hepatitis B example in Box 1 illustrates, optimistic estimates can destabilize the market, particularly for small manufacturers; suppliers lose confidence in market potential and may be unwilling to make future investments.

Very little has been done to quantify the costs and benefits of accurate forecasting. There have been limited

studies identifying logistics and warehousing costs, and some work on the potential wastage that occurs due to excess supply, but a systematic analysis has not been undertaken of the economic costs of poor forecasting on the entire supply chain and on human life. This is an area that could benefit from further research commissioned by the Working Group.

3. What Can We Learn from Other Industries, Product Lines and Markets?

Accurate demand forecasting is a challenge across a wide range of industries, and innovative solutions that have been developed to address the problem may offer important lessons for global health products. For example, low-margin, high-volume global industries such as discount retailing (e.g. Wal-Mart) have had to carefully hone their demand forecasting methodologies and develop collaborative, cost efficient yet responsive supply chains; the highly regulated electricity industry has developed sophisticated forecasting methodologies to deal with low margins and high fluctuations in demand; fast food chains, which face severe competitive pressures and low margins depend on raw materials and end products with short shelf lives and must deliver consistent products to all areas of the world, rely on forecasts which are adjusted hourly or every few minutes. While none of these industries is directly comparable to pharmaceuticals and health products, they offer useful strategies, tools and processes to inform the discussions of the Working Group.

Specific areas in health care can also provide important lessons. A great deal of work has been done on demand forecasting for reproductive health products and vaccines, for example, by UNFPA, GAVI, and the ADIP initiatives. Also developed countries and some developing countries, such as Brazil, provide good examples of how demand forecasting can be done well. The Working Group may commission research on useful practices in these areas as well.

4. Data , Analysis and Methodologies

Problems with Data and Information

Lack of reliable data on disease epidemiology and consumption patterns is at the core of demand forecasting problems. There is also very little understanding of the demand curve for heavily donor-funded markets and the variables which affect product uptake. At the country level, this area has received attention from a variety of experts, such as Management Sciences for Health (MSH)[65] and John Snow, Inc. (JSI),[66] and many tools are available for local data collection, which have been used most extensively for reproductive health products.

However, few mechanisms exist to systematically aggregate data across a range of countries and diseases or, more importantly, to analyze them to create widely trusted demand forecasts that are useful for purchasers, manufacturers and component suppliers. The few aggregate forecasts that exist are made by international agencies or NGOs that bear no financial risk for forecasting accuracy.[67]

Some argue that aggregate forecasts are only necessary for new markets and markets where there is an explicit need to stimulate demand; in most cases, they believe the market will appropriately match demand and supply and forecasting should be left to individual purchasers and suppliers. Others assert that in developing country markets, understanding aggregate demand is important to stimulate investment in product development, scale up production, leverage the purchasing power of global funders, and use scarce resources more effectively. They suggest a broader public health 'good' from understanding the aggregate demand for health products.

Regardless of whether aggregate forecasts are required on an ad hoc or ongoing basis, many agree there is an immediate need, given the rapid scale-up in resources, to create a coordinated process to gather data and provide credible aggregate demand forecasts, free of political influence, at least for major donor-funded programs. In addition to generating forecasts, the process could provide valuable analysis of demand curves for donor-funded programs, and evaluate the impact of various cost sharing mechanisms on demand.

Suggested institutional arrangements for such a process include virtual networks where purchasers and suppliers share information based on agreed upon data standards, formal consortia of stakeholders to gather and share information, contracts with existing agencies to take on the task of forecasting for different products by disease or across the board (e.g. CHAI, World Bank), contracts with market research or demand forecasting firms to enter developing country markets, or the formation of a separate entity owned by suppliers, purchasers and funders to gather and analyze available data using appropriate and transparent forecasting methods.

Problems with Methodologies

The techniques currently used to create demand forecasts are fairly simple, with high levels of uncertainty, variability and lack of transparency. They also may not be appropriate for the forecasting environment. Section III shows that there are a number of techniques that could add greater accuracy to forecasts, regardless of how or by whom data are gathered. Software to use these methods more effectively and efficiently is available but infrequently used. Many of these techniques require sophisticated forecasting expertise and are most suitable for forecasts at the aggregate level.

Based on a better understanding of methodologies, guidelines could be developed on which methods are most useful under various environmental conditions (e.g. new products with high levels of uncertainty versus existing products; countries with better time-series data versus those with poor data). Training aids on how these might be used by demand forecasters in-country and internationally could be created as part of the Group's work.

Box 3: Purchasing Cooperatives

The PAHO Revolving Fund was created in 1977 to facilitate procurement of materials for vaccine programs (e.g. vaccines, syringes, cold chain equipment). The purpose of the fund is to encourage better national planning, consolidate vaccine orders for economies of scale and assure quality control by meeting WHO specifications. The Fund establishes annual agreements with suppliers for vaccines and places quarterly orders, based on countries' demand projections; countries are invoiced for products plus a 3% service fee. Countries bear the risk of inaccurate forecasting and must inform the Fund managers at least 60 days prior to the end of the quarter that the vaccine is to be shipped or pay for cancellation charges up to the full value of the order. The operations of the Fund are imbedded into each country's immunization program and technical assistance is part of the Fund's mandate. This is a critical part of the Fund's success because it focuses on improving forecasting and all supply chain processes at the country level. Countries participate voluntarily in the Fund and may not buy all their vaccines under the Fund's contracts. The Fund reviews participation carefully ensuring that the country has good epidemiological data, cost-effectiveness studies, sustainability plans, and effective logistics systems before they are allowed to purchase through the Fund. Positive results include reduced cost of vaccines, earlier introduction to new vaccines, price stability, and better demand forecasting so suppliers can ensure adequate supply. (Freeman, P. PAHO Revolving Fund, 9 March 1999)

5. Market Innovations

Funders and Purchasers

In efficiently functioning markets, purchasers and suppliers both bear the financial and reputational risk of poor forecasting. Consequently, contracts between suppliers and purchasers frequently specify explicit incentives and penalties for poor forecasting (e.g. penalties to suppliers for long delivery times or minimum purchase guarantees by buyers). In many developing country markets, as mentioned earlier, the separation between those who pay for products and those who buy them diffuses these risks.

Some argue that accurate demand forecasting is not possible unless this fundamental funder/purchaser split is resolved through either of two very different approaches. The first is to turn donors into purchasers; the second is to integrate donor monies into national programs through budget support rather than project funding, shifting risks and rewards directly to countries. In between these alternatives are methods to encourage regional purchasing cooperatives (such as the PAHO Revolving Fund), establish framework agreements easily accessible by countries through e-procurement technology, or develop cost sharing processes between donors and recipients (see Boxes 3, 4, 5).

An added benefit of donors becoming purchasers is that significant market efficiencies could be created through consolidating purchasing power. Some donors, such as GAVI, already provide drugs and supplies to countries rather than giving cash, while others, such as PEPFAR, are moving in this direction. In the case of GAVI, a fundamental principle at its launch was that countries could procure vaccines themselves or through GAVI, but GAVI would only reimburse up to the amount for which it could have purchased the vaccine. This effectively resulted in all recipients authorizing GAVI to procure on their behalf. As a result, GAVI has been able to dramatically improve availability of vaccines and obtain lower prices through global purchasing and long term planning between suppliers, funders and countries. Pooled procurement and expected guaranteed demand have also led to the creation of a market for vaccines for developing countries, encouraging new entry by manufacturers and stimulating competition; GAVI has further been able to increase efficiency by negotiating a procurement fee of only 1.2% with its agent, UNICEF.

Box 4: E-procurement

An e-procurement initiative is being planned by the Global Fund and its partners. This system could improve market efficiency and forecasting accuracy without changing funding flows by providing easy access to framework agreements and procurement agents through which countries could order. It would also allow better data capture for forecasting. As envisioned, the system would provide incentives to countries to purchase through its global framework agreements. (Global Fund to Fight AIDS, TB and Malaria. www.theglobalfund.org)

At the other end of the spectrum is the Global Fund, which was launched with the principle that countries should have the autonomy to make their own procurement decisions under the belief that this would result in greater country ownership for programs, strengthen in-country procurement capacity, and support local suppliers who could meet international quality standards. While the Global Fund's approach may have achieved these objectives, it has also resulted in inefficient expression of funded demand. For example, rather than meeting with suppliers to negotiate on the basis of the almost one billion dollars available for the purchase of ARVs (the amount approved in current grants)[68] the Fund has dispersed this leverage to the 103 countries in which it has HIV/AIDS programs.[69]

Although attractive for creating market efficiency, any changes in purchasing arrangements must consider methods to ensure country ownership and capacity building, deal with differential pricing, and establish optimal prices for different market stages (e.g. mature markets with multiple suppliers versus markets where innovation should be encouraged).

Sustainable Financing

Given the long lead times for drug development, viable markets require sustainability and predictability in financing. In the long term, establishing domestic markets for health products that are independent of donor funding is important if private investment is expected to continue. This issue was highlighted during a recent study by the Medicines for Malaria Venture (MMV), a public-private partnership to encourage development of new drugs for malaria. The study found that the extent and timing of demand in-country for new products was influenced by considerations about financial sustainability; policy makers were reluctant to change to new, more effective and more expensive products without assurances that donor funding would continue.[70] A similar situation occurs for ARVs, where CHAI is trying to encourage countries to enter into long term agreements with suppliers, but many are unwilling to do this without greater guarantees around donor financing.

There are a number of initiatives underway to increase predictability and sustainability of aid flows including AMCs for vaccines,[71] and new financing instruments such as the International Finance Facility (IFF), proposed by U.K. Chancellor Gordon Brown and endorsed for further exploration by the G8 in Gleneagles in 2005, which will allow front loading and greater predictability in financial flows.[72] The newly proposed airline levy championed by France's President Chirac provides another mechanism to create more sustainable aid flows.[73]

Even without these mechanisms, donors could enter into guarantee arrangements with suppliers to provide assurances that sufficient funds would be available to purchase drugs and supplies. Donors could also invest in social and national insurance systems to create sustainable financing mechanisms within countries. Many countries are launching insurance schemes to provide financial protection for their citizens and donors could allocate their funds to these insurance pools in addition to directly funding interventions. The World Bank and WHO are both exploring how funders channel aid through insurance instruments, for example, funding HIV/AIDS benefits packages to provide more predictable financing.

6. Costs and Benefits

Clearly, better forecasting will come with a cost. Determining the costs and benefits, both financial and political, of approaches that could address demand forecasting challenges will be a necessary component of the Working Group's activities. Though difficult to tease out from the entire supply chain, it would be useful if this evaluation could include the health impact of improved forecasting by getting drugs and supplies to patients faster and cheaper.

The final question is: who should pay for improved forecasting? In high-income countries, where demand forecasting is done by both suppliers and purchasers, the costs for forecasting are shared de facto by these groups. A similar arrangement could be created for donor-funded markets, where the key beneficiaries – purchasers (country level and international), suppliers and donors – pool funds to pay for aggregate demand forecasting. Alternatively, donors or funders could automatically apportion a percentage of grant monies to fund forecasting. It is estimated, for example, that maintaining the supply chain costs between 4-5% of the total costs of supplies; donors could set aside .05% (illustrative only) of money allocated to supplies to support forecasting activities.[74]

Box 5: Shared Incentives and Sustainability

GAVI is exploring a method to share risk with its recipients and move towards sustainability by introducing shared financing for its recommended pentavalent vaccine. The current price of this vaccine is $10 per dose, but through discussions with new producers and a detailed understanding of the underlying cost structure, GAVI estimates that the price will fall to $3.00 over the next 10 years. It is proposing a cost sharing arrangement with countries, that will allow countries to pay $3.00 for the vaccine, while GAVI picks up the difference in cost until the ultimate projected market price is reached. GAVI will bear all the risk and rewards: if the target price of $3.00 is reached before 10 years, the countries will pay for the total costs of the vaccine; if the price is reached in 15 years, GAVI will need to pick up the difference.

Conclusion

The interviews and other inquiries conducted in the preparation of this paper have led to a broad consensus around three conclusions: First, demand forecasting is an essential element of ensuring the adequate supply of existing and new health products in developing countries. Second, attention on demand forecasting has historically centered on improving data collection at the country level; little attention has been given to aggregate forecasts at the global level and the impact of accurate forecasting on the market for drugs and supplies. Finally, better demand forecasting at the global level is necessary and urgent in order to improve the effectiveness of the substantial new monies devoted to development assistance for health.

APPENDIX

Vaccine Market Overview *(Jessica Wolf)*

Disease Overview

Existing childhood vaccines offer protection from many infectious diseases that are common in developing countries, including diphtheria, tetanus, pertussis, polio, measles, tuberculosis (BCG), hepatitis B, Haemophilus influenzae type B, and yellow fever. But every year, 27 million infants go without these vaccines, resulting in over two million preventable deaths and many more instances of disability annually. Another two million annual deaths are caused by rotavirus and pneumococcal disease, for which vaccines will soon be available.[75]

Annual Deaths, 2002[76]

Disease	Under 5	Over 5	Total
Existing Vaccines			
Diphtheria	4,000	1,000	5,000
Measles	540,000	70,000	610,000
Polio	..	..	1,000
Tetanus	198,000	15,000	213,000
Pertussis	294,000	..	294,000
Hepatitis B	..	600,000	600,000
Haemophilus influenzae b (Hib)	386,000	..	386,000
Yellow fever	15,000	15,000	30,000
TOTAL	**1,437,000**	**701,000**	**2,138,000**
Near Term Vaccines			
Meningitis AC	10,000	16,000	26,000
Rotavirus	402,000	47,000	449,000
Pneumococcal disease	716,000	897,000	1,612,000
TOTAL	**1,128,000**	**960,000**	**2,087,000**

Products & Market Development

Products: Traditional Vaccines

Historically, the vaccine market has been characterized by low-cost, off-patent vaccines supplied by several manufacturers. These "basic six" vaccines against diphtheria, tetanus, pertussis, polio, measles, tuberculosis (BCG) fall under the purview of the WHO/UNICEF Expanded Program on Immunization (EPI), and since the same vaccines were used worldwide, manufacturers were willing to tier their prices for the developing world through UNICEF. Of these, it is notable that measles and polio are often administered as part of donor-driven campaigns, whereas the remaining vaccines are generally delivered only as part of the routine immunization system. The annual cost of routine vaccines is estimated at around $50 million.[77]

Products: New and Underused Vaccines

Unlike earlier vaccines that were only pennies per dose, hepatitis B and Hib cost several dollars per treatment, and even more when combined with DTP into a conjugate vaccine. Although the overall availability of these vaccines is adequate, currently, there is only one supplier for the preferred pentavalent presentation, which has resulted in shortages of this specific formulation. As apparent in the chart below, there remains a significant gap in coverage between the newer vaccines and the traditional products.

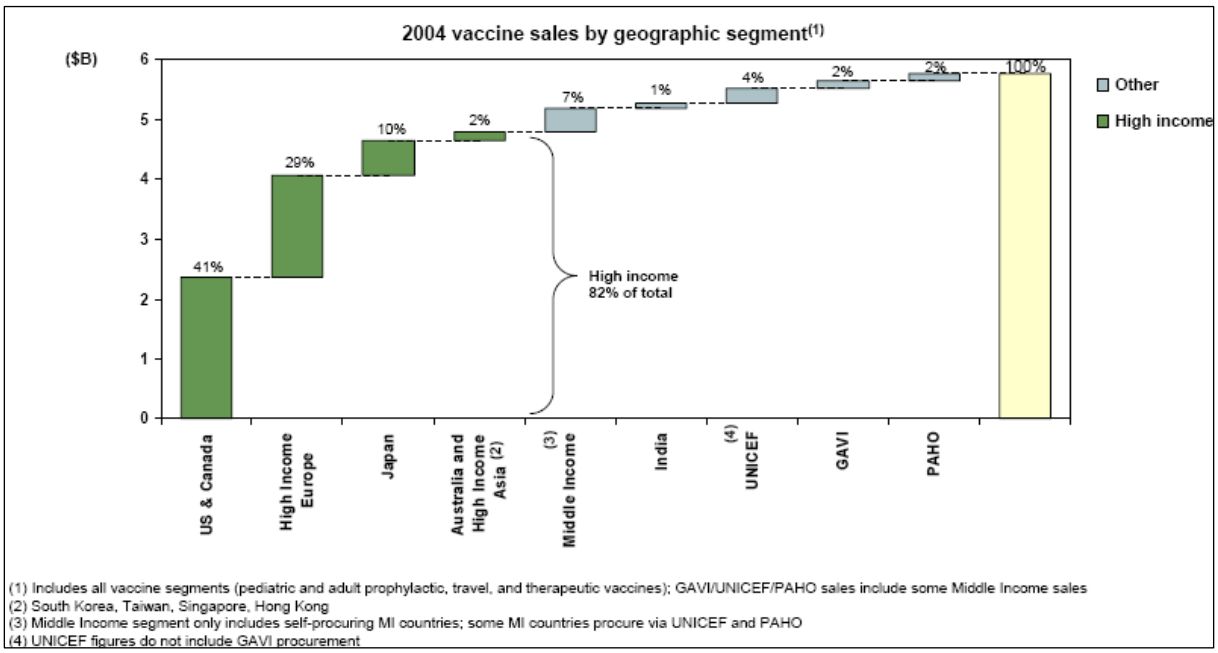
Immunization Coverage (%) Among 1-Year Olds by Region, 2003[78]			
WHO Region	**Measles**	**DTP3**	**HepB3**
Africa	63	61	29
Americas	93	91	77
South-East Asia	71	73	13
Europe	90	91	67
Eastern Mediterranean	75	77	44
Western Pacific	85	89	65

Products: Future Vaccines

Near term vaccines include rotavirus and pneumococcus, as well as meningitis and Japanese encephalitis; it is hoped that vaccines will eventually become available against malaria, HIV and tuberculosis as well. The technology required for these vaccines is more complex and costly, reflected in higher prices. In addition, the increasing divergence between the vaccine formulations and presentation required for the developing world and those for higher-income markets will continue to make it harder for companies to sell newer vaccines at or below marginal costs after recouping their investments in the developed world, as they have historically done, and presents a barrier to R&D for early stage products.

Stage of Market Development

Given the relatively low profitability of the vaccine market (in combination with a rash of corporate mergers), manufacturers have been leaving the sector. Between 1998 and 2001, 10 of 14 manufacturers ceased production of traditional vaccines, and by 2002 UNICEF was purchasing 65% of its traditional vaccines from only two manufacturers.[79] This decrease in supply – and resulting increase in price – has been compounded by the shift from wealthy countries to newer formulations (such as acellular pertussis), eliminating the differential pricing available to UNICEF. However, by acting as a source of credible demand, GAVI has helped stimulate the increased supply of new vaccines, increasing the number of manufacturers of DTP-HepB combination vaccine from just one in 2003 to eleven for 2006, and has seen a number of emerging suppliers enter the market with vaccines in the pipeline. Even so, vaccines for developing countries are still a small portion of the total vaccine market, as evidenced in the graph below.[80]



Funding Sources & Procurement Mechanisms

Most of the countries of Latin America and the Caribbean procure their vaccines through the PAHO Revolving Fund. In-country EPI advisors work with staff of the national immunization program to prepare orders on a periodic basis for specific vaccines and immunization supplies. Those requests are then aggregated at PAHO headquarters, which prepares tenders, negotiates prices, delivery dates and other contractual obligations and executes contracts. Payment is made to suppliers from the Revolving Fund. Then, when the products are delivered in-country, countries repay the Revolving Fund so that it is replenished for the next procurement round. The Revolving Fund has been effective in coordinating procurement, increasing certainty for manufacturers and reducing prices. The number of countries participating has grown from 19 in 1979 to 34 in 2003; and the capitalization of the fund has grown from the original $1 million in 1979 to $20 million in 2003.

Outside of Latin America, UNICEF is by far the largest global procurement system, supplying vaccines to 40% of the world's children. In 2004 alone, UNICEF purchased 2.8 billion doses of vaccines, worth a total of $374 million (representing 53% of UNICEF's total procurement activities).[81] It works with governments to estimate needs for specific vaccines and immunization supplies, based on existing immunization program coverage, birth rates, expected availability of funds and other factors, and then aggregates those estimates across countries for each type of product and issues tenders through an international competitive bidding process. In negotiations with suppliers, prices and a firm's track record for quality and reliability are taken into account; when possible, UNICEF also considers different suppliers of the same product in order to maintain a competitive supply environment. This security comes at a price, however – for example, fully 20% of the projected $92 million cost of measles vaccine for 2004-2006 is attributable to ensuring multiple supply sources.[82]

On the financing side, UNICEF procurement activities break down according to four business segments:[83]

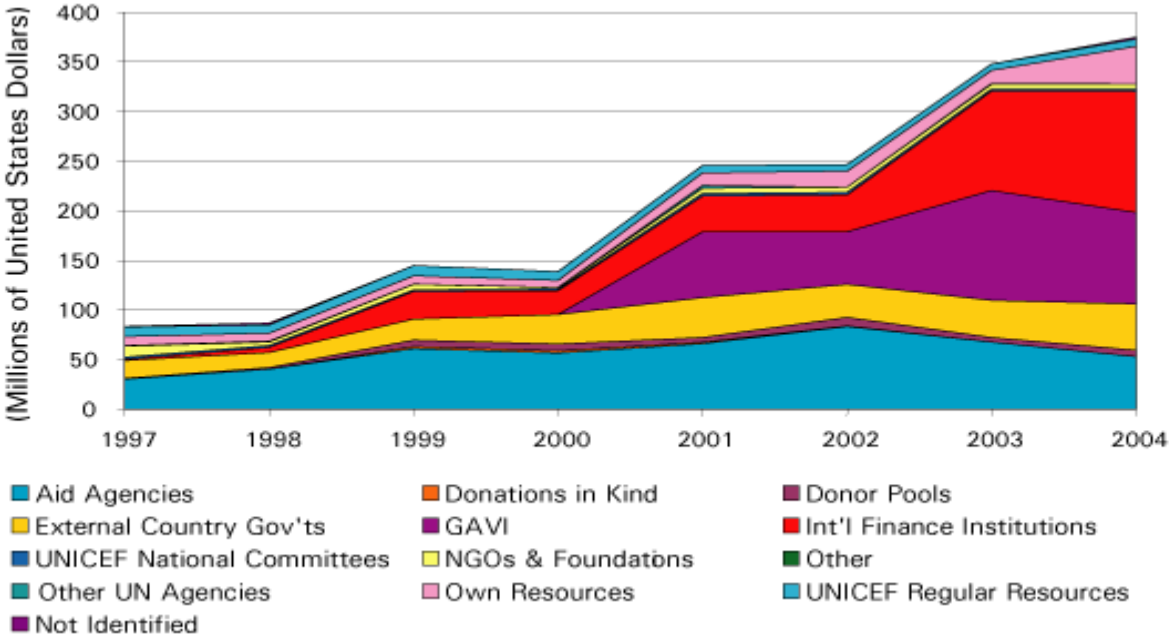
1. Traditional immunization services, disease control initiatives and outbreaks for the poorest countries, funded by UNICEF's resources and valued at $40 million in 2002;

2. Immunization services (hepatitis B, measles, rubella) for middle income countries, funded by national governments through the Procurement Services mechanism, valued at $10 million in 2002;

3. Polio eradication in endemic countries, funded by both UNICEF resources and the Procurement Services mechanism, valued at $100 million in 2002;

4. Expanded immunization services in the poorest countries to include HepB, Hib, and yellow fever vaccines, funded by GAVI through the Procurement Services mechanism at a value of $130 million in 2004.[84]

Source of UNICEF Funds for Vaccine Procurement[85]



UNICEF procures most vaccines under long-term arrangements typically lasting one to two years (but which can last up to five) that consist of agreements with manufacturers on the commercial terms for products, such as prices, delivery schedules and packing requirements, so that when an order is placed, it can be delivered rapidly. As a part of this process, UNICEF also provides the vaccine industry with forecasts for vaccine requirements, but these are only indicative and do not form an enforceable contract.

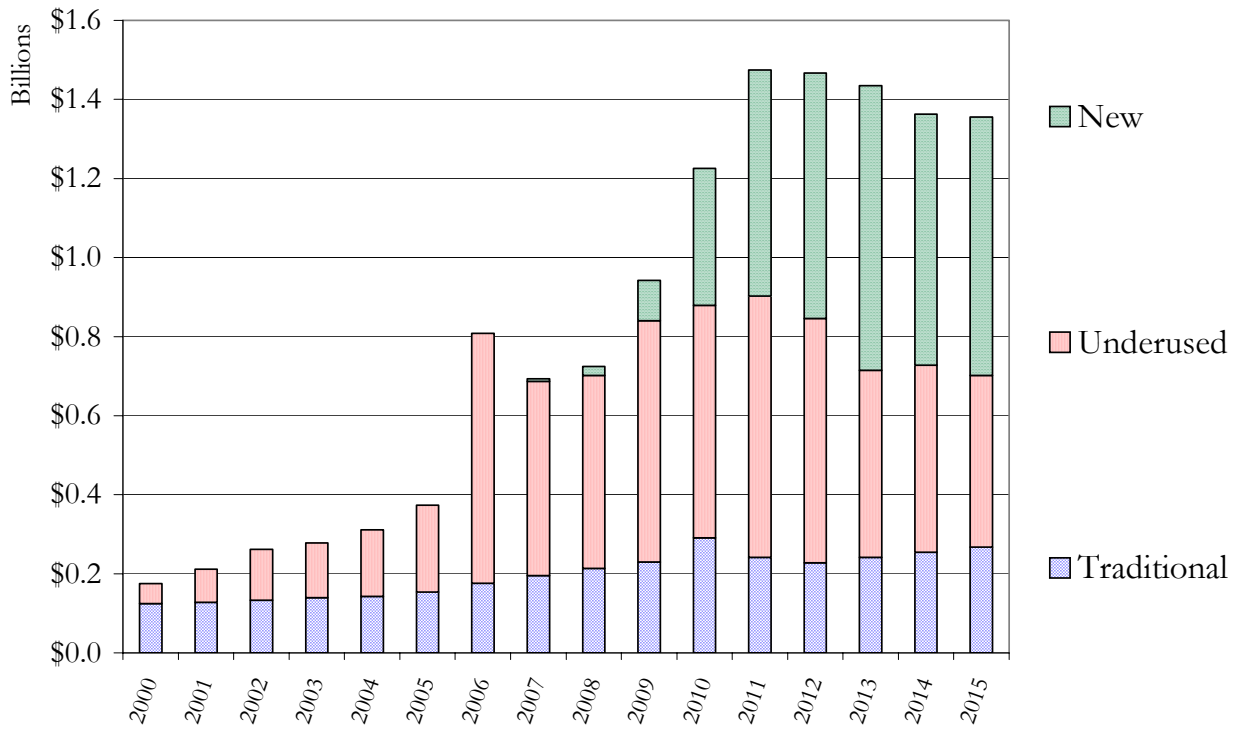
Without binding long-term contracts, though, potential suppliers cannot confidently invest in long-term productive capacity, resulting in higher prices for developing countries, lower use and occasionally supply constraints. But while UNICEF has moved toward longer contracts where possible, its ability to sign multiyear purchase agreements is constrained by donor funding cycles where guarantees are typically made on an annual basis. However, the GAVI Fund has been able to give UNICEF multiyear funding "in trust" to support a multiyear contract by setting aside money for future payments. The launch of the International Finance Facility for Immunization (IFFIm) has increased the stakes by leveraging additional donor dollars on the private capital markets through government bonds to raise money for GAVI. By providing a predictable source of frontloaded funds, this mechanism has the potential to lower vaccines prices if the supply strategy is adjusted accordingly to benefit from this opportunity.

Product Pricing & Projected Demand

UNICEF Projected Demand by Product Type (2005)[86]

Vaccine	*Presentation*	*Total Projected Doses*	*Weighted Average Price per Dose*	*Expected Demand*
BCG (ampule/vial)	20 dose	109,000,000	$0.09	$10,137,000
DTPw	10 dose vial	90,000,000	$0.14	$12,330,000
DTPw	20 dose vial	43,000,000	$0.12	$5,246,000
DT	10 dose vial	1,700,000	$0.10	$164,900
Td adults	10 dose vial	9,500,000	$0.07	$665,000
TT	10 dose vial	91,100,000	$0.11	$9,929,900
TT	20 dose vial	68,500,000	$0.05	$3,630,500
OPV	10 dose vial/tube	65,000,000	$0.12	$7,475,000
OPV	20 dose vial/tube	835,000,000	$0.11	$87,675,000
Measles (lyophilized)	10 dose vial +	150,000,000	$0.17	$24,750,000
Yellow Fever (lyophilized)	5 dose vial +	4,800,000	$0.58	$2,784,000
Yellow Fever (lyophilized)	10 dose vial +	10,900,000	$0.80	$8,720,000
Hepatitis B (recombinant)	1 dose vial	1,620,000	$0.41	$664,200
Hepatitis B (recombinant)	2 dose vial	3,300,000	$0.36	$1,188,000
Hepatitis B (recombinant)	6 dose vial	5,600,040	$0.62	$3,488,825
Hepatitis B (recombinant)	10 dose vial	65,500,000	$0.27	$17,685,000
MMR Urabe Strain Mumps (lyophilized)	10 dose vial + diluent	800,000	$1.36	$1,088,000
MMR Urabe Strain Mumps (lyophilized)	1 dose vial + diluent	100,000	$1.70	$170,000
MR (lyophilized)	10 dose vial +	3,000,000	$0.49	$1,464,000
Meningitis A&C (lyophilized)	50 dose vial + diluent	3,000,000	$0.37	$1,122,000
DPT-HepB (recombinant)	10 dose vial	22,500,000	$1.25	$28,125,000
DTP+ Hib (lyophilized)	10 dose vial +	201,000	$2.80	$562,800
DPT-HepB+ Hib (lyophilized+ liquid)	2 dose vial	23,000,000	$3.60	$82,800,000

Vaccine Costing Projections[87]



State of Demand Forecasting

UNICEF forecasts vaccine demand on a five year rolling basis, reaching a high of 80% accuracy in 2004.[88] UNICEF's demand forecasts are largely based on needs and are partially advocacy driven (reflecting targets rather than unbiased projections), creating an incentive to overestimate the demand, and since they are not bound by their contracts they do not share the risk of excess supply costs with industry. Some of the other constraints include a lack of standardization and consistent application of assumptions, estimates based on inaccurate country information, and the lack of a clear methodology for determining whether or when countries will introduce new vaccines.

Partly to address these concerns, initiatives like the Accelerated Development and Introduction Plans for pneumococcus and rotavirus vaccines are attempting to recognize the pivotal importance of having an accurate forecast of demand, particularly in the late stages of product development when manufacturing facilities are built and thus supply capacity established.

Malaria Market Overview *(Daniella Ballou-Aares & Kris Jacob)*

Malaria Financing & Demand: Summary Table

Annual epidemiological impact: 300m – 500m affected, approximately 1 million deaths

- **Estimated Annual need by product type (2007):**[89]

Product Type	*Number of Units*	*Value per Unit*	*Total Value*
LLINs	31.5m	7	$220m
ACTs	1102m doses	1.07	$1,108m
Rapid Diagnostic Testing	776m tests	.07	$54m
Total			$1,380m

- **Expected Annual Financing Available ($, 2007)**

Donor	*Estimated 2007 Funds*
Global Fund to Fight AIDS	$1,200m
President's Malaria Initiative (US)	$135m
World Bank	$170m (est)[90]
Total	$1,505m
Share allocated for health products (based on Global Fund share)	*49% ($750m)*

- **Annual expected demand by product type (2007):** Considering funds expected from major donors, $750m will be available for drugs and commodities. This will fulfill approximately 54% of the total annual need ($1.38 billion).

Disease Overview

Annually, malaria acutely affects 300 - 500 million people and kills approximately 1 million.[91] Malaria deaths are most significant among pregnant women and children, and occur despite the existence of highly effectives treatment therapies. The primary barrier to preventing malaria sickness and death has until recently been financial resources. However, with funds devoted to malaria prevention and treatment growing rapidly, supply and distribution challenges have become significant and immediate barriers to scale-up.

While the figures above demonstrate the significant global impact of malaria, even more people may be affected by the disease than previously estimated. A recent study by scientists at the University of Oxford has determined that 500 million may be a conservative estimate of the number of people affected by malaria. The study found that, while estimates of malaria incidence are fairly accurate for Africa, the number of cases in South East Asia and Western Pacific are underestimated. Specifically, the study discovered that approximately 25% of total cases occur in those two regions. While it is important to know the size of the problem to properly articulate how much money is needed to tackle the problem, we will use the Roll Back Malaria figures in this paper, keeping in mind that their figures are likely conservative estimates.[92]

Products

Products: Prevention

There exists a set of preventative measures that are known to be highly effective in malaria control. They include the use of indoor residual spraying, insecticide treated nets and intermittent preventative treatment during pregnancy. The most significant market associated with these interventions is for insecticide treated nets, and in particular long lasting insecticide-treated nets (LLINs), an innovative new product now available in the markets. These nets, rather than having to be re-treated with insecticide, every three to five months, remain effective for three to five years.[93]

Products: Treatment

In the case of infection, treatment has traditionally been chloroquine-based, but due to increased resistance this treatment is no longer effective in many regions. Artemisinin-based combination therapies (ACTs) are today the treatment of choice for malaria, and thus far, have proven to be highly effective. Unfortunately, these new drug formulations are much more expensive than the chloroquine-based treatment they are slowly replacing.

ACTs are the largest donor funded malaria product market.

Stage of Market Development

If there exists today both a method of prevention and a method of treatment, why does malaria affect, and even kill, so many people? There are several challenges: insufficient financing, poorly functioning distribution and delivery mechanisms, and finally, inadequate supply. The shortage of supply presents the most immediate challenge related to demand planning, because financing is growing quickly and supply has not yet caught up to meet the rapidly growing demand for products. Specifically, there are significant shortages in the supply of both long-lasting insecticide treated mosquito nets and artemisinin-based treatments. Both are nascent products and markets, and without an estimate of demand, manufacturers have been slow, at least initially, to ramp up supply.

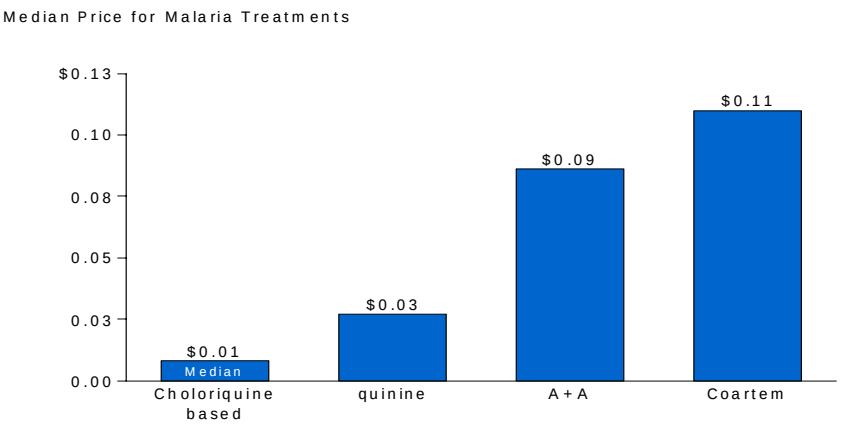
Total Product Need

In 2007, the products required to successful treat and prevent malaria will be primarily ACTs and long-lasting insecticide-treated nets. As shown below, these markets, if fully funded, will reach hundred of millions of dollars, with the market for ACTs alone having the potential to reach $1.2 billion.

Item	Demand Estimate (Millions)	Unit Price ($)	Total ($) (Millions)
LLINs	31.5 units	7	220
ACTs	1102 doses	1.07	1180
Rapid Diagnostic Testing	776 tests	0.07	54
Intermittent Preventive Treatment in Pregnancy	39.7 treatment courses	0.164	6.5

Product Pricing

New malaria products are more expensive than the older products they replace. For example, long-lasting nets are often twice as expensive, at $4 - $7 per net versus $2 - $4 for the conventional variety of nets. Although the long term cost effectiveness of the long lasting nets is higher, the upfront higher can have a significant impact on buying behavior.



The figure above shows unit prices for a range of anti-malarial treatments, indicating the significant range in product pricing that exists, with chloroquine typically at one-tenth the price per unit of the most common ACT (Coartem by Novartis).

Financing Available

Financing for malaria has historically been far below needs, fulfilling only $300 million of the $3 billion in estimated international funding required in 2005. However, available funding is forecast to grow rapidly over the next two years – and by 2007 will reach more than 50% of needs, or $1.5 billion. The largest share of this funding will be from the Global Fund to Fight AIDS, TB and Malaria. The Global Fund contributed $135 million to malaria programs in 2004, 45% of total funding. This is expected to reach $1.2 billion by 2007, where it will continue to hold the majority share of funding. A new large source of funding will be the President's Malaria Program, which is projected to reach $135 million in 2007 and $300m in 2008. The World Bank's Malaria Booster Program will also provide funding, which expects to spend $500m over the next 3 years.

Actual Demand

Assuming that all of the funds expected above are available in 2007 ($1.5 billion), then based on historical averages, 49% of these funds will be for drugs and commodities. Therefore, approximately $750m would be available to finance ACTs and long-lasting insecticide- treated nets (LLINs). This equates to 54% of the total need for the year ($1.4 billion). It is important to keep in mind, however, that there is a lag between funding allocations and spending of between 1-2 years.

State of Demand Forecasting

What is the current state of demand forecasting?

Estimating the number of people in need of both ACTs and long- lasting nets is far more straightforward than determining actual demand for products. This is because the need is simply the number of people affected, while demand is the number of treatments that will in fact be purchased – either with resources from international donors, national public sectors, or by private individuals. For new malaria products, the need has been far greater than the effective demand because there have been insufficient funds available for the purchase of these goods.

As shown in the section on financing, international donors represent the largest share of malaria funding for the two new main products – LLINs and ACTs. Thus, the best manner by which to forecast demand, currently, is by looking at funding. Reports on future expected financing and demand by major donors are closely watched by suppliers. To forecast demand at a local level, it is likely that suppliers combine this

information with country level data they are able to collect directly from ministries of health or other major local purchasers.

This demand data, however, has a high degree of uncertainty. Both the timing of funding receipt by countries, and its translation into actual orders are typically uncertain. Even more fundamental, initial funding commitments by donors may change – both in their scale or the nature of expected expenditures. Country level data remains uncertain because of poor planning systems at the local level.

Who does it?

It does not appear that the pharmaceutical industry has invested significantly in forecasting demand for anti-malarial products. It can be assumed that this is the result of company expectations that the market is relatively small and low margin. Private market research firms also tend to neglect tropical diseases, such as malaria, for the same reasons. The major actors in forecasting today are major international donors and technical agencies. The Roll Back Malaria Partnership's Malaria Medicines and Supply Service (MMSS) and the Global Fund to Fight AIDS, TB and Malaria all provide public information - albeit sporadically - that can assist supplier efforts to forecast demand. MMSS, in particular, has undertaken to collect country level demand and supply information on LLINs and ACTs. However, public reporting on a consistent basis does not yet occur. Furthermore, the consistency and reliability of this information over the medium to long term remains uncertain.

Gaps

The main problem with existing malaria data is a lack of granularity and consistency in data available. For example, while the Global Fund to Fight AIDS, Tuberculosis and Malaria provides information on planned funding for malaria grants by country – disaggregating this information in a consistent manner by product and year is not currently feasible. Similarly, while MMSS has undertaken to collect country level demand data for ACTs and LLINs, this data is relatively short term in nature and subject to uncertainties in the underlying data from financing entities and countries.

A significant challenge in enhancing demand forecasting for malaria is the lack of financial and human resources invested in forecasting. While major pharmaceutical companies, for instance, typically have large market research and brand management teams that invest a significant amount in forecasting, the international agencies currently involved in malaria demand forecasting are extremely small.

HIV/AIDS Market Overview (*Daniella Ballou-Aares & Kris Jacobs)*

HIV/AIDS Financing & Demand: Summary Table

- **Annual epidemiological impact (2005):** 39 million infected, 3.1 million deaths
- **Annual need by product type (2007):**[94]

Product Type	*Number of Patients*	*Value per Unit*	*Total Value*
ARVs (first line)	6.5m	$140/yr - $300/yr	$940m - $2bn

Significant additional product markets exist for opportunistic infection treatment, second line ARVs, diagnostic devices and testing, but insufficient data available to estimate each market.

- **Expected Annual Financing Available ($, 2007)**

Donor	*Current 2007 Commitments*	*2007 Funding Required*[95]
Global Fund to Fight AIDS	$2.3bn	
PEPFAR (US)	$3bn	
World Bank	$1.1bn (est)[96]	
Total	$6.4bn	$11.5bn
Share allocated for health products	*55% ($3.5bn)*	*55% ($6.3bn)*

- **Annual expected and financed demand by product type (2007):** Considering funds expected from major donors, $3.5 billion will be available for drugs and commodities.

Disease Overview

In 2004, there were approximately 39.4 million people living with HIV/AIDS AIDS and 3 million who lost their lives to the disease.[97] In that same year, more than 5 million adults and children became infected with HIV.

UNAIDS Region	**People Living with**	**Deaths Due to HIV/AIDS,**
Sub-Saharan Africa	25,400,000	2,300,000
South/Southeast Asia	7,100,000	490,000
Latin America	1,700,000	95,000
East Asia	1,100,000	51,000
North America	1,000,000	16,000
Eurasia	1,400,000	60,000
Western Europe	610,000	6,500
Caribbean	440,000	36,000
North Africa/Middle East	540,000	28,000
Oceania	35,000	700
Total	*39,400,000*	*3,100,000*

There is no cure for AIDS, only a lifelong treatment regimen once a person is infected. Treatment has historically been very expensive, and therefore only with the significant cost reductions that have occurred since 2001 has it become a viable option for many people in developing countries, where AIDS takes its greatest toll. Sub-Saharan Africa, for example, contains 25.4 million of the 39.4 million people living with HIV/AIDS. Of those 25.4 million, there are approximately 4.7 million people in need of ARV treatment. Yet only 11% of those in need are currently receiving it – approximately 310,000 people.[98]

Products

Products: Antiretroviral Drugs

Antiretroviral drugs (ARVs) are the primary medication used in the treatment of the HIV retrovirus. ARVs essentially make it difficult for HIV to attack the immune system. Combinations are used so that, even if the virus becomes resistant to one of the ARVs, the others suppress the resistant strain. Compliance to treatment is essential to prevent the spread of resistant strains.

While there are many sub-categories of ARVs, the most significant product distinction is between first and second line treatments. First line treatments are used as the initial treatment regimen for patients. Patients often build a resistance to these treatments, or may even have a strain of AIDS that is resistant to first line treatment from the onset. Second line treatments are critical to keeping patients alive over the long term, but remain significantly more costly and complicated to administer than first line treatments. Second line treatments are also expected to suffer from shortages in the short term.

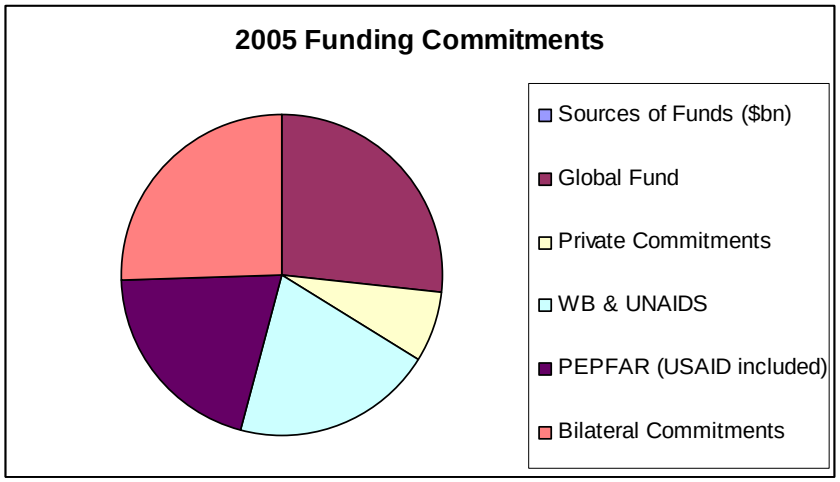
Other Products

A wide range of products are needed to effectively treat HIV/AIDS, and even in a resource-poor setting products beyond ARVs are required. Products that play an essential role in treating HIV/AIDS include treatments for opportunistic infections, rapid tests and diagnostic devices for CD4 count and other indicators of infection level.

Total Product Need

The total number of patients under the age of 50 in need of treatment reached 6.5 million people across low-income and middle-income countries in 2005. Assuming that all of these patients received ARVs at the most competitive prices ($140 per year), the total need would be $910 million; at a higher, but more likely average cost of $300/year, the potential market in developing countries would be $2.0 billion.[99] Developing countries currently pay in the range of $140 - $500/year for first line treatments.[100]

Financing Available



In 2005, the Global Fund was the largest funder of AIDS programs, providing $1.38 billion of the $5.1 billion in available funding. PEPFAR was the second largest funder in the year with $1 billion. In 2007, the Global Fund is expected to account for $2.3 billion of total funding, or 18% of the $12.8 billion required in that year ($11.5 billion required from international sources). PEPAR is expected to contribute approximately $3 billion that year, with a total expected committed $15 billion over a five year period between 2003 and 2008.[101] The amount that will actually be disbursed is uncertain because Congress must provide the final approvals for funds.

The total funding committed to date for 2007 is $6.4 billion, while total estimated international funding requirements for that year is $11.5 billion. Assuming that 55% of funding is for drugs and commodities, this translates into commitments of $3.5 billion for the purchase of ARVs, drugs to combat opportunistic infections, diagnostics, rapid tests, and other products used in the treatment of AIDS. It is not known how that funding will be distributed across the numerous products required to treat AIDS.

State of Demand Forecasting

What is the current state of demand forecasting?

In developed markets, strong demand forecasting exists for ARVs and other AIDS products, but in developing markets it is still limited and much of the best data is proprietary and so not publicly available to all players. While data for ARVs is limited, demand forecast data for other AIDS product markets – such as treatments for opportunistic infections, testing and diagnostics – is almost nonexistent.

Who does it?

Epidemiological forecasting, in the developing world, is being undertaken by UNAIDS. WHO's AIDS Medicines and Devices Service (AMDS) is the most active organization in product demand forecasting and is creating a Global Price Reporting Mechanism to record product prices. Probably the most comprehensive source of data is the Clinton Foundation, but their data is currently proprietary. Procurement agents such as UNICEF, IDA and IAPSO also collect market data and develop proprietary forecasts.

Gaps

One of the greatest challenges in HIV/AIDS product markets is that treatments are complex and rapidly changing. There are a large number of different drugs and producers to contend with. Further, the suppliers are disaggregated, and don't have much bargaining leverage with suppliers. Another challenge is the wide range of products required, which would require incorporating and estimating a wide range of data to accurately forecast demand across all product areas.

Tuberculosis Market Overview *(Daniella Ballou-Aares & Kris Jacobs)*

TB Financing & Demand: Summary Table

- **Annual epidemiological impact (2005):** 8 million with active TB, 2 million deaths. 27% of those in need of treatment are receiving it.
- **Annual need by product type (2007):**[102]

Product Type	*Number of Patients*	*Value per Unit*	*Total Value*
Multi-drug therapy (e.g. rifampin, ethambutol, isoniazid, pyrazinamide)	8 million	$108	$864 million

- **Expected Annual Financing Available ($, 2007)**

Donor	*Estimated 2007 Funds*
Global Fund to Fight TB	500m
Total	800m
Share allocated for health products	*35% ($280m)*
Funding from domestic resources	1,200m

- **Annual expected demand by product type (2007):** Considering funds expected from major donors, $280 million is expected to be available from international drugs and commodities. Based on historical data domestic resources (public and private) will spend at least an additional $200 - $400 million for TB products.

Disease Overview

Tuberculosis is the most common major infectious disease in the world. It affects more than 2 billion people, or one third of the entire world's population. The vast majority of these people have latent TB, but even so, more than 8 million people develop active TB annually and more than 2 million people die from the disease. The majority of prevalence and mortality occurs in the developing world, primarily Southeast Asia and sub-Saharan Africa.

TB was considered to be under control as recently as twenty years ago. However, a variety of factors, including the HIV/AIDS pandemic, has brought about a resurgence of TB. As HIV weakens the immune system, an individual is much more likely to become infected and sick with TB. In fact, TB is a leading killer amongst people with HIV/AIDS, especially in Africa. TB accounts for 13% of AIDS-related diseases worldwide, and is the leading cause of AIDS-related deaths in Africa.[103]

A cost-effective cure for TB has existed for more than fifty years, and yet, today, only 27% of those in need of treatment are receiving it.

Treatment

DOTS is directly observed treatment, short-course, and is the treatment course advocated by the WHO to combat active TB. Treatment for active TB consists of a combination of drugs. A typical treatment for non-drug-resistant TB includes two months on isoniazid, rifampin, pyrazinamide, and ethambutol, followed by

two months of just isoniazid and rifampin. Medication can be given either daily, or two or three times a week, but then at higher dosages.[104]

The reason four drugs are administered is to ensure that no resistant strain emerges. This is also why it is so important to ensure compliance with TB treatment. If patients don't complete the entire treatment course for TB and instead discontinue treatment when their symptoms subside, there is the chance that they will relapse and the new TB strain in their body will be drug resistant. This has led to multi-drug resistant strains, which are becoming increasingly common. One of the primary purposes of DOTS is to ensure people's compliance with their entire treatment course to prevent the creation of drug resistant strains.

Products

Products: Drugs for the treatment of TB

As noted above, a combination of the treatments below are used to treat TB. All products are off patent and available from multiple generic producers. Recent supply shortages in the markets for the raw materials, which are dominated by two main suppliers, have led to recent product price increases.

Market Size

The total market for TB was estimated at $450 million per year in 2004 and expected to reach $670 million by 2010.[105] There have been significant efforts to encourage the development of a new MDR TB product, expected to have a market of $200 - $400 million per year.[106]

The total potential market for TB drugs can be calculated based on the cost for an average treatment. The following table shows the cost per drug per complete 24-week treatment cycle per patient:[107]

Drug	Adult Daily Dose	Intermittent (Three Times Weekly) Treatment	Cost per Dose ($)	Total Cost per Treatment per Patient ($)
Rifampin	10	24 weeks * 10 doses/day = 1680 doses	0.04	67.2
Ethambutol	20	8 weeks * 20 doses/day = 1120 doses	0.022	24.64
Isoniazid	5	24 weeks * 5 doses/day = 840 doses	0.004	3.36
Pyrazinamide	23	8 weeks * 23 doses/day = 1288 doses	0.01	12.88
			Total =	108

Based on the data above, the full potential market is 8 million treatments at $108 per patient, or $864 million.

Financing Available

TB differs from HIV/AIDS and malaria in that the majority of the required resources come from domestic sources. In 2007, domestic funding of TB programs is expected to reach $1.2 billion and international funders are expected to provide and additional $800 million.[108] If all of this funding is in fact available, sufficient resources will be available for effective TB control. However, uncertainty remains in both domestic and international resource allocations with many competing priorities, particularly HIV/AIDS, putting a drain

on national health budgets. With TB cases on the rise, particularly multi-drug resistant varieties, additional funding resources may be required.

Further, even with proper funding for drugs, the scale-up of treatment faces the constraints of shortages of trained staff, lack of political commitment, weak laboratory services, inadequate management of MDR-TB, and inadequate management of TB co-infection in people with HIV/AIDS. These further constraints must be dealt with in order to achieve universal treatment coverage, and funding to remove these constraints must be taken into account.[109]

State of Demand Forecasting

Estimating the total market for TB requires inclusion of multiple funders and buyers. The Global Drug Facility (GDF) for TB is the single largest developing country mechanism for TB products, which purchased $31.5 million of drugs in 2004.[110] This initiative of the Stop TB Partnership works to improve the procurement of drugs to combat TB. As such, they try to assess the demand for TB drugs. Other than the GDF, the only organization that really takes a global approach to demand forecasting is the Global Fund to Fight AIDS, Tuberculosis and Malaria. Demand forecasting tends to happen at the level of funding, and there is very little global demand forecasting in part because of the proportionately large share of domestic (rather than donor) financing. TB has been relatively neglected on the global humanitarian scene, probably due to the lack of recent innovations in fighting the disease, but has gained recent attention with the launch of the Stop TB Partnership's new campaign to raise an additional $31 billion over the next ten years.

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