Advance market commitment for pneumococcal vaccines: putting theory into practice
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Abstract Markets for life-saving vaccines do not often generate the most desired outcomes from a public health perspective in terms of product quantity, quality, affordability, programmatic suitability and/or sustainability for use in the lowest income countries. The perceived risks and uncertainties about sustainably funded demand from developing countries often leads to underinvestment in development and manufacturing of appropriate products. The pilot initiative Advance Market Commitment (AMC) for pneumococcal vaccines, launched in 2009, aims to remove some of these market risks by providing a legally binding forward commitment to purchase vaccines according to predetermined terms. To date, 14 countries have already introduced pneumococcal vaccines through the AMC with a further 39 countries expected to introduce before the end of 2013.

This paper describes early lessons learnt on the selection of a target disease and the core design choices for the pilot AMC. It highlights the challenges faced with tailoring the AMC design to the specific supply situation of pneumococcal vaccines. It points to the difficulty – and the AMC’s apparent early success – in establishing a long-term, credible commitment in a constantly changing unpredictable environment. It highlights one of the inherent challenges of the AMC: its dependence on continuous donor funding to ensure long-term purchases of products. The paper examines alternative design choices and aims to provide a starting point to inform discussions and encourage debate about the potential application of the AMC concept to other fields.

Introduction
The prevention of disease through vaccination with efficacious and safe vaccines is one of the most cost-effective public health interventions. However, often the markets for vaccines do not generate the most desired outcomes from a public health perspective in terms of product quantity, quality, affordability, programmatic suitability and/or sustainability, particularly when it comes to serving the poorest populations. Economic factors may hinder or delay the clinical development of candidate products as well as prevent manufacturing of licensed vaccines at sufficient scale to respond to these needs. Manufacturers face competing interests when making investment decisions and they perceive demand from developing countries as very uncertain. While the need for and the willingness to adopt new vaccines exist, resources to sustainably fund such products are often missing. Manufacturers thus find this market segment very risky and less attractive. An Advance Market Commitment (AMC) for vaccines aims to make the market for vaccines in developing countries more attractive through a legally binding commitment to purchase vaccines according to predetermined terms. As some of the risks are removed, the vaccine industry is encouraged to increase investments to stimulate the development and manufacture of target products.

Different models have been designed to create market-oriented incentives to support the development and introduction of appropriate health technologies for developing countries. Many have remained academic exercises, but the AMC moved from theory to practice with a pilot AMC for pneumococcal vaccines launched in 2009. While it is still early to assess the efficiency and effectiveness of this pilot, this paper discusses lessons learnt on moving from the theoretical concept to implementation. It provides a starting point to inform discussions and encourage debate about the potential applications of the AMC concept to other interventions.

The pilot AMC
An AMC for vaccines gained public attention with a report by the Center for Global Development in April 2005. The report proposed to create incentives for commercial investments in research, development and manufacturing of vaccines for developing countries through a legally binding pledge by donors to pay a certain price for a new vaccine if it is developed and desired.

A pilot AMC for pneumococcal vaccines was announced in February 2007 and formally launched in June 2009 with a joint pledge of 1.5 billion United States dollars (US$) by the Governments of Canada, Italy, Norway, the Russian Federation and the United Kingdom of Great Britain and Northern Ireland, and the Bill & Melinda Gates Foundation. The key design features and the functioning of the AMC for pneumococcal vaccines are described in Box 1. The GAVI Alliance, a public–private partnership created to increase access to immunization in poor countries, and The World Bank co-led the design of the pilot and they implement it together with the United Nations Children’s Fund (UNICEF) and the World Health Organization (WHO). By placing the AMC on its balance sheet, The World Bank effectively guaranteed US$ 1.5 billion in AMC funding for the purchase of pneumococcal vaccines. Meanwhile, the GAVI Alliance serves as the secretariat for the AMC and has committed to support eligible
Box 1. Design and functioning of the Advance Market Commitment for pneumococcal vaccines

The pilot Advance Market Commitment (AMC) offers a legally binding commitment to support the market of targeted pneumococcal vaccines with US$ 1.5 billion of funds for which vaccine manufacturers can bid. Interested manufacturers compete over successive tenders to supply a share of the annual forecasted demand of vaccines (which is expected to increase over time and reach around 200 million doses per year at peak). In exchange, the AMC provides a fraction of the US$ 1.5 billion directly proportional to each manufacturer’s supply share.

Each manufacturer must commit to supply its annual share of doses for 10 years at a maximum price of US$ 3.50 per dose (i.e. “tail price cap”) which was set close to the estimated marginal cost of production at the time of the AMC design) to be paid by GAVI and GAVI-eligible countries. Each manufacturer’s share of AMC funds is disbursed as a subsidy per dose additional to the tail price – bringing the total price up to US$ 7 for approximately the first 20% of vaccine doses procured from each manufacturer. This “AMC price” is set with the aim to enable companies to quickly recover incremental investment costs incurred to serve the GAVI market.

Donors pay for results

Donor AMC funds will be spent only if a suitable vaccine comes to market and if this product is demanded by GAVI-eligible countries. A limited purchase guarantee, equivalent to 45% of one year’s committed supply, is offered to each manufacturer. Thus, countries must desire the vaccines, have the health systems in place to introduce them, and must be able to pay their share of the final price, jointly with GAVI.10

Lessons learnt

The evaluation and choice of a target vaccine for the pilot AMC was led by an independent expert committee of internationally recognized experts in public health, epidemiology, industrial economics, vaccine development, financing and law.11 In 2006, this committee recommended pneumococcal vaccines as the most suitable candidate for a demonstration AMC mainly because of the expected magnitude of the vaccine’s health impact on the target population and the ability to leverage an already existing robust pipeline of efficacious vaccines (given two candidate vaccines were in advanced stages of development). The committee also emphasized the ability to test rapidly the viability and effectiveness of the AMC concept in influencing industry and donor behaviour.12 In fact, as work progressed, it became clear that the AMC model was broad and required considerable work to be tailored to the specific characteristics of the target market, i.e. the pneumococcal vaccine market. The following examples illustrate some of the challenges faced.

Competition and early supply

The pilot AMC targeted two objectives simultaneously; (i) motivating first-generation suppliers – with nearly licensed vaccines – to increase manufacturing capacity and (ii) spurring development of new vaccines by second-generation suppliers, hence fostering competition in the long term. Yet, since both generations of suppliers compete for AMC funds on equal terms, second-generation suppliers may have little incentive to participate as they will require more time to enter the market and AMC funds may be depleted by the time they do. The main rationale for this design was to ensure adequate supply capacity to serve imminent demand – allowing countries to introduce these life-saving vaccines as fast as possible. In addition, setting equal conditions for all manufacturers was a way to minimize concerns of preferential treatment. In practice the pneumococcal conjugate vaccine market is currently dominated by two companies, GlaxoSmithKline and Pfizer, and the market will be truly competitive when and if additional manufacturers enter the market. RETrospectively, in similar markets, one might find ways to encourage competition more rapidly. One option could be to target first- and second-generation suppliers separately, perhaps with different simultaneous AMCs.

A “level playing field”

Engagement of both first-generation suppliers was considered highly desirable to ensure sufficient and secure supply in the early years of the programme. Consequently, the terms of the AMC offer (in particular the tail price cap) being equal for all manufacturers, ensured that both suppliers were sufficiently encouraged to participate. As they had different production technologies, strategic objectives and costs, it may have been more efficient to provide or negotiate tailored contracts with the two manufacturers, rather than shape a “one size fits all” contract. Although this option was discussed, AMC donors

countries to purchase the product. Some of the expected benefits of the AMC are outlined here.

Assured quality

To be eligible for AMC funding, vaccines must meet minimum product specifications, as stipulated in the Target Product Profile developed by experts from WHO in 2007 for the AMC pilot. WHO guided manufacturers in their development efforts by defining additional minimal characteristics of target products suitable for immunization programmes in developing countries.6,7

Early supply

By providing some assurance of recoupment of investments, the AMC encourages manufacturers with a nearly licensed product to scale up supply capacity to serve GAVI-eligible countries faster (the historical lag between roll out of new vaccines in industrialized countries relative to low-income countries has been ≥ 10 years).3

Lower purchase price

While the AMC ensures that companies quickly receive funds to cover investment costs, beneficiary countries and their co-sponsors (in this case GAVI) pay a price close to the estimated marginal cost of production right from the start. Without an AMC, prices for new vaccines (e.g. hepatitis B vaccines) have tended to remain high in the first years following market introduction and decline only after several manufacturers enter the market.7

Incentives for competition

Unlike other “pull-funding” mechanisms (e.g. prizes) that reward the first supplier, the AMC intends to create a market of multiple manufacturers, to provide healthy competition and sustainable supply in the long term. The terms are non-exclusive: any manufacturer with a qualifying product can bid to supply a share of the annual forecasted demand for pneumococcal vaccines. Companies compete on the long-term price offered and on product quality. Competing bids are also assessed to ensure sufficient supply to meet demand and provide supply security over time.

Policy & practice

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Bull World Health Organ 2011;89:913–918
doi:10.2471/BLT.11.087700

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did not want to establish differential and potentially preferential terms for different suppliers.

**Changing environment**

One of the intrinsic difficulties of the AMC is to establish a long-term, credible commitment in a constantly changing unpredictable environment. For instance, the AMC for pneumococcal vaccines is set up to encourage development of 200 million doses of annual production capacity for target pneumococcal vaccines, an amount slightly more than the estimated peak annual demand from GAVI-eligible countries at the time of the AMC set-up. A reduction in demand would mean the AMC was not used to its full potential, which would in turn reduce the likelihood of participation by late market entrants. Also, some AMC funds would for some time lie unutilized – since disbursement of the US$ 1.5 billion is based on the supply of 200 million doses annually for ten years. Additionally, any drop in demand for which there are existing supply contracts would lead to an inefficient use of AMC funds as suppliers would be left without paid-for and dedicated but unused production capacity.

While uncertainties about vaccine uptake at country level may be unavoidable, the AMC could potentially have done a better job at enhancing overall demand predictability. For instance, to foster demand stability and predictability, the AMC contracts could have fixed the list of eligible recipient countries over the duration of the programme, rather than allowing for changes as occurred when the GAVI Board revised the country eligibility policy in November 2009. While this decision threatened to reduce projected peak demand, the GAVI Board subsequently decided to provide continued access to pneumococcal vaccines under the AMC terms and conditions to all GAVI countries that were eligible at the time of signature of the legal agreements (although only the lowest-income countries would benefit from GAVI financial support). A second example of unpredictability is that GAVI pays a considerable proportion of the vaccine price and funds are contingent upon continuous donor contributions. Consequently, the actual level of funded demand depends on GAVI’s ability to raise sufficient resources over time. This highlights one of the inherent challenges of the AMC: while attempting to reassure industry of the viability of the developing country market for vaccines, the AMC still heavily depends on donor funding to ensure long-term purchases of available and much needed products. In future, the ability of the final buyer to purchase the target product over time may need to be considered as a central design and selection criterion when choosing a target intervention. For future AMCs, it might also be desirable to explore the coupling of an AMC with long-term and predictable donor commitments to the buyer’s budget as well as innovative, less pro-cyclical sources of funding.

**Discussion**

While some analyses of the AMC for pneumococcal vaccines are available, it is too early to draw any firm conclusions on its efficiency and effectiveness. For now, the AMC pilot stands out as a successful collaboration between different partners. To date 37 countries have been approved for funding support from the GAVI Alliance and 14 countries have introduced pneumococcal vaccines into their national programmes. By 2013, a total of 53 countries are expected to have introduced pneumococcal vaccines through the AMC agreement and GAVI financial support. The first of these introductions happened within approximately one year of introduction of the same products in high-income countries.

Because of its innovative design, the AMC has received a tremendous amount of attention from the international community, governments, industry and academia. This has led to increased awareness and attention to vaccines in general, and specifically to pneumococcal vaccines, as a powerful prevention measure.

Moreover, experience with this AMC suggests that long-term donor commitments can be made credible to industry and induce manufacturers to sign long-term binding commitments themselves to supply a fixed amount of vaccines per year at a predetermined price. This is unprecedented as, historically, industry has entered only into good faith agreements of three years with no binding obligation to supply. Since the signature of the legal agreements, four manufacturers – GSK, Pfizer, the Serum Institute of India and Panacea Biotech – have publicly disclosed their formal agreement to the AMC terms and conditions. As a result of a first tender issued in September 2009, UNICEF entered into supply agreements with GSK and Pfizer under which both manufacturers supply 30 million doses annually each for 10 years from January 2012 for GSK and from January 2013 for Pfizer. Both manufactures have also committed to supply additional doses in 2010 and 2011 while scaling up production capacity. A second tender for additional doses is currently underway.

The supply price of US$ 3.50 per dose can also be considered a significant achievement. This is more than a 90% reduction in price compared with the European Union and the United States of America, where average public prices are 40 Euros and US$ 96, respectively. New this reference price for the lowest-income countries may impact prices charged for other segments of the market. Some authors suggest that, given the cost structure in vaccine production, both consumers in developing countries and high-price markets may benefit from such a tiered pricing scheme.

Donors and policy-makers in different fields – within and beyond health – follow the implementation of this AMC to assess its value and applicability to other products affected by similar market failures. For example, the United Kingdom Department for International Development started to explore AMCs to support low-carbon technology development. There is also ongoing work, led by Canada and the United States of America and supported by The World Bank, to develop AMCs and other pull mechanisms in the context of agriculture and food security. Whether an AMC is the most efficient and cost-effective tool compared to other push- and pull-funding options depends on the specific problem. Based on the lessons described in this paper, we can draw some tentative conclusions.

**Conclusion**

The AMC concept is broad and needs careful and flexible crafting to address the specific problem efficiently and effectively. The analysis of a particular technology’s demand and supply landscapes must drive project designers to define an adequate AMC contract ensuring appropriate incentives for desired goals.
The AMC pilot for pneumococcal vaccines provides insights for products in a similar market. In this case, we learnt that there are trade-offs between the objectives of ensuring sufficient manufacturing capacity to serve imminent demand and establishing a competitive market in the long term. Yet, this AMC tells us little as to whether the mechanism would effectively work to encourage commercial investments in research and development for new vaccines in early stages of development or whether a similar model can be applied to other types of pharmaceutical products. It is likely that an AMC is more easily established in markets where a single entity is in charge of pooling and purchasing large volumes of demand for a predefined set of countries and is thus able to make a credible commitment. While vaccines for the lowest-income countries are often purchased through some form of global or regional pooling mechanism, this is not typically the case for pharmaceutical products which are more often individually purchased by countries. A prominent exception is the dominant role that UNITAID plays in purchasing a high proportion of paediatric antiretrovirals.

This AMC pilot also shows the importance of predictability, particularly of sufficient funding commitments from donors and/or beneficiary countries to pay the long-term purchasing price of vaccines in addition to the AMC envelope. Ongoing monitoring and evaluations scheduled for the coming years will provide further information about the value of this AMC and its applicability to other interventions.

竞争利益声明：None declared.
Resumen

Compromiso de mercado avanzado para vacunas neumocócicas: poniendo en práctica la teoría

Los mercados de vacunas que salvan vidas no suelen generar los resultados más deseados desde una perspectiva de salud pública, en términos de cantidad, calidad, viabilidad del producto, así como de idoneidad y/o sostenibilidad programáticas para su uso en los países con menores ingresos. Es frecuente que los riesgos e incertidumbres percibidos sobre la demanda financiada sostenible de países en desarrollo conlleven a la desinversión en el desarrollo y fabricación de los productos adecuados. La iniciativa piloto Compromiso de mercado anticipado (CAM) para vacunas neumocócicas, que se lanzó en 2009, pretende eliminar algunos de estos riesgos de mercado mediante la creación de un compromiso legalmente vinculante para la compra de vacunas de acuerdo con condiciones predeterminadas. Hasta la fecha, ya son 14 los países que han introducido vacunas neumocócicas a través del CAM y se espera que otros 39 países las introduzcan antes de finales del 2013.

Este documento describe las lecciones anteriormente aprendidas sobre la selección de una enfermedad objetivo y las elecciones de diseño principales para el CAM piloto. Destaca los retos a los que hay que enfrentarse para adaptar el diseño CAM a la situación de suministro de vacunas neumocócicas específica. Señala la dificultad – y al aparentemente temprano éxito del CAM – de establecer un compromiso creíble, a largo plazo, en un entorno impredecible y constantemente cambiante. Destaca uno de los desafíos inherentes del CAM: su dependencia de la financiación donante continua para asegurar compras de productos a largo plazo. El documento examina las opciones de diseño alternativas y pretende proporcionar un punto inicial para informar las discusiones y promover los debates sobre la aplicación potencial del concepto AMC a otros campos.

Referencias
