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Review

Apples and oranges? Can second generation vaccines become as low cost as generic medicines?

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ABSTRACT

The recent approval of multiple new vaccines and their introduction in many Gavi countries have been the impetus for efforts to reduce the costs of these vaccines. In this paper, we provide an overview of the main cost drivers for bringing second generation vaccines and compares these, where relevant, to the cost of bringing generic medicines to market. We argue that the main cost drivers for vaccine development are fixed, implying that second-generation vaccines do not lead to the same price reduction as normally seen with generic drugs. Lastly, we provide recommendations of the areas within vaccine development that could support further cost reductions.

Contents

1. Introduction

The Sustainable Development Goals and associated targets explicitly refer to the need for affordable vaccines [1]. With the relatively recent approval of multiple new vaccines – including

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human papilloma virus (HPV), rotavirus (RVV) and pneumococcal conjugate (PCV) that are considerably more expensive than traditional vaccines, the desire to scale up availability in Gavi countries motivates global efforts to bring the price down. The question is often raised as to why generic medicines are produced so much more cheaply, when compared to the innovator medicine, than second generation vaccines, when compared to the innovator vaccine.

This article illustrates the limitations of the analogy by explaining the main cost drivers for bringing second generation vaccines to market and by highlighting, where relevant, how those differ from the costs of bringing generic medicines to market. While it does not address pricing per se, which is often driven by additional market and commercial factors, a better understanding of what drives vaccine costs can help inform policy makers, donors as well and the general public on measures that may ultimately also contribute to affordable and sustainable prices.

2. Definitions – vaccines and medicines

Vaccines are biological products produced using living organisms and involve the manipulation of genetic material and living animal, bacterial, or yeast cell cultures. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface antigens (usually protein or polysaccharide). The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system more easily recognizes and destroys any of these microorganisms that it later encounters. Vaccines are either prophylactic or therapeutic.

First generation vaccines are the first marketed vaccines for a specific disease or combination of diseases or address a previously targeted diseases through a new technology that brings improvement (e.g. less injections, increased duration of protection, improved safety). Second generation vaccines can be marketed for the same diseases (or combination of disease) as first generation vaccines but can be produced through a different and potentially less costly manufacturing process. What is specific to vaccines compared to non-biological medicines is that any new vaccine is considered a new biological entity, whether or not it is manufactured through the same technology as previously available vaccines. Hence, there is no such thing as generic vaccines, only so called bio-similars (highly simiar in terms of structure, function and clinical effect to the innovator product). All vaccines need to go through human studies and bear related costs in order to be registered. Furthermore, many second generation vaccines are likely to be patented e.g. new and improved adjuvants suitable for vaccines aimed at preventive or therapeutic vaccines, improved delivery mechanisms and delivery routes (e.g. oral or mucosal).

This renders many aspects of vaccine development, production and regulation distinct from medicines. Medicines are designed to prevent or treat disease. Drugs are substances used as medications and designed to produce a specific reaction inside the body. Most medicines are chemicals and produced by chemical synthesis with standardised production processes.[2] First-generation or originator medicines are the first products in a therapeutic category authorized for marketing on the basis of the documentation of their efficacy, safety and quality, according to requirements at the time of authorization. The originator products are usually patented and have a brand name e.g. Panadol.

[2] Statements about medicines and generics apply only to those based on chemicals. Biologics (and biosimilars) have a unique set of issues that are more similar to vaccines.

Generic medicines are chemically identical to to the branded counterpart and contain the same active ingredients. These products are often known by their International Non-proprietary Name (INN) e.g. paracetamol. When the patents for the originator products expire, companies often apply to make generic versions. The companies need to submit information proving that their product is bio-equivalent to the brand-name drug, but they do not have to repeat most of the expensive and time-consuming human studies to show the drug to be safe and effective.

3. Research, development, manufacture and regulation

3.1. Biological standards, assays, animal models and clinical trials

In vaccines, there are a number of tools that could help speed clinical development and in turn help reduce costs. However, there has been underinvestment in these tools, in particular for emerging infectious diseases and diseases of poverty [2]. Biological standards (i.e., written descriptions of quality requirements and materials used as benchmarks in scientific tests to demonstrate quality) and assays can support evaluation of products throughout the development cycle and enable comparisons between different vaccines. They can help with reproducibility and replicability of data. Appropriate [3,4] animal models are also required before testing in humans to better understand history of disease and demonstrate proof of concept. For many vaccines, there is a dearth of appropriate models. Development of such models can be both costly and time consuming [4,5]. With regard to clinical trials, recognizing that the number of participants is dependent on many factors, including incidence of disease, sensitivity of case definition, and potential effect size, vaccines are mostly used for prevention, and unlike most medicines, they are usually given to healthy, asymptomatic individuals, whereas medicines are most often given to try to cure disease. Where side-effects may be tolerated proportionally to the severity of the disease that the medicine is treating, vaccines need to demonstrate a higher level of safety than medicines. Also, demonstrating efficacy at preventing disease in a healthy population can require very large numbers of subjects which increase costs [6].

3.2. Quality assurance and control

Oversight for vaccines includes regulations that cover how each process must be conducted from discovery to licensure and every production step from bulk manufacturing to packaging, with stringent limitations on deviations from the authorized processes [7]. Dozens to hundreds of tests are conducted in the course of vaccine production. Any changes to production, whether in scale, process, or presentation, require a regulator's approval to prove that these changes do not alter the characteristics of the final product [8].

At every stage during the vaccine manufacturing process, quality control (QC) steps are needed, incurring costs and increasing timelines for production. For complex multi-valent or combination vaccines, such as 10- and 13-valent conjugate pneumococcal vaccines, hundreds of QC checks are required for approval of each production batch. These requirements lead to extremely high start-up and production costs, long lead times, stringent and labor intensive quality assurance processes, and consequently are often seen as barriers to market entry for new manufacturers [9]. While there are also significant QC milestones related to drug formulation, including dissolution testing and analysis of both raw materials and synthesized product, additional quality control measures for vaccines, such as lot release, which tests the quality on each individual batch of vaccines before they are released for the market, pose additional costs [10,11].

Good Manufacturing Practice (GMP) is part of the quality assurance mechanisms that ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use. Compared to medicines, vaccine production usually requires additional investments for consistent GMP-compliance [12].

3.3. Regulation

Generic medicines are "copies" of first generation medicines. When all patent issues are resolved, a generic medicine can be brought to market in less than five years at considerably lower cost than originator products [8]. That is because generic medicine manufacturers typically do not need to invest in research or pre-clinical phase of development and instead rely on an abbreviated regulatory pathway that precludes the need to invest in clinical trials.

In some countries, in order to gain market approval for the sale of generic medicines, regulatory authorities require manufacturers to demonstrate that their generic copy is bio-equivalent – therapeutically equivalent – to the originator product. Bio-equivalence trials are designed to compare the release, absorption and elimination of the active ingredients and to demonstrate similarity of the two formulations. But these trials are generally conducted in less than a hundred subjects and over a much shorter period of less than one year.

In the case of vaccines, there are no "generics" per se and the regulatory approval process for second-generation or follow on products is similar to that of the first-generation. So, in contrast to generic drug manufacturers, second-generation vaccine manufacturers must develop their own production processes and invest in additional clinical trials, because even the simplest of biologicals, such as small and well-characterized proteins, must be tested for specific efficacy and safety that cannot be determined by simple bio-equivalence. As such, second-generation vaccines are also likely to be patented, because they will often include new and improved technologies, such as improved delivery mechanisms and routes.

To ensure continuing safety of the vaccine product and manufacturing process for vaccines, regulatory agencies also require manufacturers to submit samples of each vaccine lot to test for potency, safety and purity. The lot-by-lot testing and release take months (more than a year for some vaccines), and the demonstration of consistency in manufacturing and final products often requires a period of years and is made at considerable cost [13].

4. Production

4.1. Manufacturing

Manufacturing vaccines is a complex process when compared to medicines. For medicines, the methods used to produce the active ingredients are mostly those of chemical synthesis that can be standardized into industrial scale production lines without heavy or long industrial development efforts. For vaccines, the processes are inherently more labour intensive, less predictable, do not easily lend themselves to automation, and usually require several time consuming scale-up steps. Cultivation for example, includes growth of the appropriate organism, which needs close monitoring for contamination.

Further, the inherent variability of living organisms, means that biological products require special quality assurance mechanisms, beyond those already mentioned. For example, vaccine manufacture requires the handling of live organisms which are sometimes pathogenic. The release of these agents not only poses the threat of possible contamination or cross-contamination, but in some case poses a serious danger to human health requiring the workers, environment, and all the materials to be well protected [14]. This is true with regards to emerging epidemic diseases but also to well to know pathogens like yellow fever.

4.2. Facilities

While the cost of physical infrastructure required to manufacture medicines can be quite low [15], facilities for vaccines cost 50–500 M USD per antigen based on design, automation, segregation, and other factors and as much as 700 M USD for multiple vaccines [6].

New facilities are increasingly dedicated for each specific vaccine produced and are almost always constructed "at risk" in terms of financial investment as it is before results of clinical trials and regulatory approval have been obtained. Although some developing country vaccine manufacturers build manufacturing facilities at reduced prices due to lower real estate, power, and building costs, other costs including the vaccine production equipment and risks are similar to those manufacturers based in wealthier countries. Nevertheless, because of the labour intensive nature of vaccine production, in particular with regard to quality assurance and quality control, the lower wages paid in developing countries can reduce costs of production [16].

4.3. Complexity

In medicines, generic manufacturers can find cost advantages in employing more efficient production processes. They can also take advantage of on-going innovation and industry learning so far as it is in the public domain. The more stringent regulatory requirements for vaccine production means that it is often difficult for vaccine manufacturers to make changes after market approval. They therefore cannot always take advantage of learning and technological advances without repeating clinical trials.

Such savings have a significant impact on overall cost. An analysis of the key cost drivers for new pneumococcal conjugate vaccines showed that process efficiencies in manufacturing could have a greater impact on reducing production costs than geographic location [17]. However, how quickly and effectively manufacturers optimize and implement process improvements to innovative technology will have a significant impact on the overall costs and timelines of the development continuum. Continuing work to improve established processes, even after licensure of the vaccine, is challenging but can lead to significant increases in product yields that in turn will reduce costs [18].

5. Market factors

5.1. Competition

Competition creates innovation, including on ways to bring down costs. Historically there has existed significantly greater competition in the medicines markets than in the vaccine market, in particular in areas where there are high volume or financially attractive markets. Within HIV anti-retroviral markets, which are high volume, for example, each drug tends to have five or more competitors with additional competition within and even between treatment categories. As a result, there is greater competition to maintain and gain market share, which ultimate serves to lower prices [19] including by driving innovation in production efficiency. In contrast competition in the vaccines market is largely limited, due to historical barriers to entry and significant regulatory and quality approval requirements. Also, in the vaccine sector, often the total vaccine production capacity in the short to medium

term is not sufficient to satisfy demand, as has been the case with HPV and PCV. Prices therefore remain high unless there a sufficient number of manufacturers to engender competition.

5.2. Fixed and variable costs

While generic medicines are mainly driven by variable costs, which change depending on output volumes, such as labour, energy costs and raw materials, for second-generation vaccines, fixed costs for vaccines, which remain constant regardless of output level, remain high in comparison to most non-biological medicines for both trials and manufacturing. This is because of safety and efficacy testing requirements, complexity of manufacturing, limited scope for incremental process improvements and lack of an abbreviated regulatory pathway for market approval [13].

5.3. Pricing tactics

In the vaccine industry, where fixed costs are high, the absolute size of the market must be large enough for producers to spread their average costs over large volumes over a reasonable timeframe. Similarly, given that fixed costs are high, in order for new manufacturers to achieve low average costs, they must gain a large market share in a short timeframe. This is a significant barrier to the market, since a new entrant to a vaccine market will be aware that their entrance leads to intensified price competition, trigger price wars and erode profitability levels. In addition, marketing is also used as a pricing tactic for example to try to position one vaccine as superior to another, even when clinical effectiveness may be similar.

5.4. Intellectual property rights

For pharmaceuticals, patents and other forms of intellectual property (IP) provide first-generation manufacturers with the means to limit competition for a period of time, allowing them time to recover investments.[3] That said, in the majority of cases, once a patent has expired, competition is possible. While perceived to be less of an issue for existing vaccines, the impact of intellectual property rights on R&D and manufacturing of newer vaccines and the related cost require vaccine by vaccine investigation [20]. In some cases, when a manufacturer holds patents on biological entities and processes, other manufacturers in many cases work around this by developing alternative techniques that are not protected and which circumvent specific patented technology, however this can take time. Furthermore, vaccine manufacturing processes also require considerable "know-how" that even if not patented acts as a high barrier to entry for new manufacturers [21].

5.5. Risk and uncertainty

Market uncertainty comes about from a lack of clarity in demand for the coming years. It affects how manufacturers allocate fixed costs and how efficiently they produce and ultimately their certainty of profit. Uncertainty, actual or perceived, is caused by changes in epidemiology (e.g. fluctuating disease burden and varying effectiveness of control initiatives cause fluctuations in demand), financing (e.g. reductions in donor pledges), policy changes (e.g. shifts in government priorities) or supplier selection (procurers choose a competitor), delays in implementation (e.g. bottlenecks that delay products from reaching target populations or delays in in-country project implementation). Other factors that impact the level of uncertainty are the size of the manufacturer's upfront investment, level of risk aversion, managerial practices, and the competition.

Demand uncertainty in combination with required large fixed capital investments, prevents manufacturers from wanting to compete in certain markets. When producers are uncertain about future demand, they adjust product prices so as to "front-load" costs or earn back fixed costs over a shorter time period [22,23]. The magnitude of the inefficiency risk premium depends on the level of perceived uncertainty, the length of period in which a manufacturer is exposed to it and the length of the production process.[4]

6. Conclusions

Despite many similarities, the biological nature of vaccines makes their development, production and regulation very different from medicines and there are no "generics" per se. While generics drugs approval results from demonstrating "bioequivalence" to the innovator product, this is not an option for vaccines, where second generation are de facto treated from a regulatory prospective as new to market. Thus, while we have seen the price of some generic medicines fall by more than 80% of their first generation equivalents, similar reductions for second generation vaccines are unlikely without addressing the fundament drivers of cost [21].

As such, the prospect of "generic like" drug prices may not be feasible for vaccines given current technologies and market dynamics. While increased competition also helps drive process innovation and has a positive impact on cost (and ideally price), a step change will require fundamental shifts in vaccine technologies and how they are developed, regulated and even manufactured [24]. This will require investment across the value chain including, where relevant, in biological standards and assays to speed investigation or proof of concept, platform technologies to speed research and development, regulatory science to speed approvals [25], and manufacturing to reduce costs while maintaining quality. Gains in these areas would potentially have a positive effect on costs of first-generation vaccines.

Conflict of interest

Author declares that there is no conflict of interest.

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[3] The use of flexibilities allowed in the original TRIPs Agreement, including the compulsory licensing of a patent, and international efforts (such as the Medicines Patent Pool) to make patents available to interested entities can help reduce the negative impact IPRs may have on the cost of medicines.

[4] Manufacturers seek to optimize costs by choosing the right level of production (continuous, non-continuous, on demand) and the level inventory that minimizes costs, including the cost of stock outs. A longer production process means that the manufacturers will be exposed to uncertainty for a longer period of time, increasing the probability that their production versus inventory decisions are sub-optimal.

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