SUSTAINABILITY OF IMMUNIZATION PROGRAMS: TRADITIONAL FUNDING AND FINANCING ALTERNATIVES VERSUS INNOVATIVE PRACTICES.

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Table of Contents

MAIN CONCLUSIONS

- Although there are alternatives such as volume purchases through PAHO's Revolving Fund or the GAVI alliance to improve the population's access to vaccination processes, these strategies have been insufficient to ensure equitable and sustainable access for middle- and low-income populations.

- For GAVI-eligible countries, there is an urgent need for a mechanism to ensure the financial sustainability of immunization programs once they graduate from GAVI support but do not have the income level to access them on their own.

- Novel mechanisms are urgently needed, especially in middle-income countries with no guaranteed sustainable access to immunization programs, including cost-effectiveness studies of vaccines in immunization programs and evidence-based decision-making to ensure long-term sustainability.

- There is an urgent need for countries to increase their technical-scientific capacity, which requires governments to commit to improving and strengthening those political and financial aspects that guarantee the participation of national laboratories in the sustainable supply of vaccines to immunization programs, as well as in the research, development, and production of new vaccines.

- Alternative strategies should be explored that harness the power of competition, avoid arbitrary market segmentation, and recognize government responsibilities, such as tiered pricing, including new variables for tiering.

- There is also a need for an articulation where public laboratories in middle and low-income countries are integrated into the development of vaccines against some emerging and re-emerging diseases (1) which may not be included in the production lists of many manufacturers because they only address problems in less developed countries.

SYNOPSIS

Every year, infectious diseases kill 14 million people, and most of these deaths are among poor people living in developing countries, especially children under the age of five. Most of these diseases are preventable or easily treatable. However, many drugs and vaccines that can prevent this morbidity and mortality are too expensive for developing countries to afford (2).

Despite being one of the most efficient, successful, and cost-effective health investments in history, almost one in five deaths of children under five years of age is still caused by a vaccine-preventable disease, and only 12 infectious diseases account for 20% of the entire global burden of disease and disability (3). More than 22 million children, mostly in developing countries, do not have basic immunization schedules (4).

Vaccines against diseases of global public health importance have not yet been incorporated into routine immunization schedules in most developing countries. Many countries do not have sufficient financial resources to introduce these vaccines into their immunization programs, and their use is limited to the private sector. Thus, the neediest children cannot access the new vaccines, causing inequalities and inequities between populations, and marked differences in the vaccination plans of the countries (5).

Immunization has eradicated smallpox and nearly eradicated polio, substantially reduced the number of measles and rubella cases worldwide, and reduced the incidence of disease, disability, and death from other preventable diseases (6). It is estimated that the annual use of recommended vaccines for children prevents up to 3 million deaths per year worldwide, with an even more significant number of cases of disease and disability prevented.

One of the strategic objectives of the Global Vaccine Action Plan was to extend the benefits of immunization equitably to all people; however, despite some progress, this goal is far from being achieved, especially for low- and middle-income countries. A fundamental principle of immunization is that everyone has an equal right to these services, regardless of who they are or where they come from.

Despite the efforts made by international organizations for a more equitable acquisition of vaccines, there are still many gaps that make this access inequitable and often ineffective for the actual demand for vaccination that would be necessary for middle-income and low-income countries (7). The inequity of this situation is even

more severe given that the highest mortality rate from vaccine-preventable diseases is found in middle- and low-income countries:

It is estimated that more than 90% of deaths from pneumococcal infection, 95% of deaths from Hib, and 80% of deaths from hepatitis B occur in developing countries (8).

The adoption of new vaccines by middle- and low-income countries (where the burden of these diseases is the highest) has been slower than in high-income countries (9); even though among public health interventions, immunization programs are the most sanitary efficient, i.e., those that achieve the most significant benefits based on the cost incurred (1), for many countries access to vaccines depends on the decisions of private companies, when it should also be a governmental responsibility.

However, it is critical to assess the long-term financial sustainability of immunization programs and sustainability when incorporating new vaccines. This measure should be a vital issue for governments to address, as discontinuation of a vaccine due to lack of funding can have severe consequences for disease control and health outcomes in terms of equity. On the other hand, if funds are diverted from other health programs to pay for the new vaccine, it will be necessary to deploy careful planning to ensure that other health program priorities and services are not affected (10).

Immunization is one of the most efficient health interventions, but as countries develop new vaccines at higher costs, these will need to be introduced into vaccination schedules. It entails more significant expenditure by governments to keep up with vaccination schedules. Still, there will be a lag in immunization capacity in those countries where governments cannot access these new vaccines. On the other hand, this development of new vaccines also increases operational, and personnel costs related to vaccination programs. Therefore, many studies have evaluated the effectiveness and cost-effectiveness of childhood immunization programs in reducing the impact of vaccine-preventable diseases in low- and middle-income countries (11). These studies have shown that immunization programs prevent millions of deaths and illnesses, producing a sizeable economic impact by reducing countries' expenditures on treating diseases and their sequelae and avoiding lost productivity (12). In addition, vaccines bring health benefits to the immunized child and the community through herd immunity. Immunization programs prolong the population’s life expectancy and contribute to countries' economic growth (13).

Because of the above, there is a need to propose more effective, equitable, and long-term sustainable alternatives for access to innovative vaccines in Latin American and Caribbean countries. In this way, essential gaps could be closed for the population to access health care, mainly for children, when reducing the high mortality and morbidity rates related to immunopreventable diseases in Latin American countries, most of which are middle and low-income, could be reduced, which would have a positive economic impact on the region.

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1. DESCRIPTION, ANALYSIS OF THE SUBJECT, AND SUGGESTED RECOMMENDATIONS

1.1Aspects to be considered for financing immunization programs in the region

It is becoming increasingly evident that economic constraints are only one of the obstacles to vaccine availability in low- and middle-income countries. These countries must consider several factors when formulating sustainable immunization programs over time; therefore, technical assistance to create effective, robust, and sustainable national immunization programs is almost as important as financial considerations. For this reason, emphasis should be placed on creating models in which international support is based on national capacities and development needs and not exclusively on income (7).

A significant obstacle in the region is the low spending on research and development for vaccine production. Only 10% of global expenditure is allocated for pharmaceutical research and development for diseases that account for 90% of the worldwide disease burden (3). The costs associated with vaccine development and the intellectual property rights that protect them are very high in vaccine production. In Latin America, very few laboratories have the technical capacity to do research and develop these vaccines.

Also, and as a consequence of the lack of political decisions and resources, very few laboratories for vaccine production in the region have been able to modernize their facilities adequately or have standardized the application of good manufacturing practices and quality control systems, which conflicts with the demands of self-sustainability, uniformity in product quality, price competitiveness, responsibility in the fulfillment of product delivery and attention to the need for new vaccines, necessary to access their production (1).

Additionally, in the Region of the Americas, the deteriorating socio-economic situation in countries such as Venezuela has significantly impacted their health infrastructure, including their immunization services. The resurgence of measles has also led the region to lose measles elimination status, just two years after it was

achieved in 2016 (7). The resulting measles and diphtheria outbreaks have spread to other countries in the region. They have made it essential to strengthen and ensure the sustainability of immunization programs throughout the region to ensure the minimum coverage necessary to prevent the spread of these and future outbreaks.

In addition, the Region of the Americas is characterized by an advanced demographic transition, with an average life expectancy of 77 years and a total fertility rate (2.0 children per woman) very close to the replacement threshold. Population aging and the increased prevalence of noncommunicable diseases are generating growing financial pressures on health systems and heightening concerns about the sustainability of programs, especially in lower-income countries with higher fertility rates (14).

Thus, dependence on external aid and the presence of development workers have varied widely in the Region. In some countries, the participation of actors such as the Global Alliance for Vaccines and Immunization (GAVI) has been decisive. It continues to be so, although, in countries with a strong presence of international cooperation, this is expected to decrease progressively in the coming years (14).

On the other hand, the costs attributable to immunization programs include both direct costs and those of the health system, including immunization personnel, injection supplies, transportation and cold-chain, outreach services, personnel training, social mobilization, and promotion activities, as well as costs associated with disease surveillance, management of the immunization program, operating costs (maintenance of the cold chain and equipment, building operating expenses and utilities), etc. (13).

Taking this into account, future strategies to improve access to vaccines will have to address the main obstacles to their acquisition, which consist of simplifying the regulatory pathways for biosimilar vaccines, managing intellectual property barriers, and reducing barriers and timelines for the entry of multiple new suppliers through technology transfer and know-how (8). In addition, obstacles related to disincentives to innovation for the generation and improvement of existing vaccines must be overcome and work on the sustainability of these processes.

Finally, the cost-benefit of immunization programs, which has been amply demonstrated in the literature, should be considered. It is widely recognized that population health is critical from a public health and economic perspective, as healthy people contribute to economic growth. Vaccination can contribute substantially to improving population health and thus strengthening economic growth. Reductions in mortality and morbidity also contribute to increased

consumption and GDP. Therefore, assessing the value of vaccines and vaccination programs should evaluate the direct impact on health and health care and a broader impact considering their relationship with economic growth.

In addition to this, the decrease in sick leave, which leads to lower productivity, must be considered. Similarly, many of these immunopreventable diseases generate long-term permanent neurological sequelae, such as deafness, blindness, epilepsy, and paralysis, which undoubtedly highlights the tremendous economic impact on health systems of not carrying out timely immunization programs for their population.

The Global Alliance for Vaccines and Immunization (GAVI) evaluated the impact of vaccination, including the effects on cognitive development, educational attainment, labor productivity, income, savings, investment, and fertility, and stated that the rate of return was expected to be 18% by 2020. Vaccination prevents some 5 million deaths from chickenpox, 2.7 million from measles, 2 million from neonatal tetanus, 1 million from whooping cough, 600,000 deaths from polio annually, and six hundred thousand deaths from polio and some 300,000 from diphtheria. In economic terms, over the 2011-2020 period, the savings are estimated to amount to more than US$6 billion in treatment costs, US$145 billion in productivity not lost, and US$231 billion in lives saved (12).

Therefore, when generating a sustainable program that guarantees immunization, the obstacles present in the region should be considered due to its social, political, and economic particularities. However, it should also be considered that immunization is an investment that will continue to provide health and economic benefits in the long term.

2. Traditional Vaccine Financing Methods

2.1 The Vaccine Alliance – GAVI

The GAVI Alliance is a public-private partnership created to improve health in the world's poorest countries. The Alliance brings together donor and developing country governments, WHO, UNICEF, the World Bank, the vaccine industry in both industrialized and developing countries, technical and research agencies, civil society, the World Bank, the GAVI Foundation, the World Health Organization, The Alliance brings together donor and developing country governments, WHO, UNICEF, the World Bank, the vaccine industry in both industrialized and developing countries, research and technical agencies, civil society, the Bill & Melinda Gates Foundation, and other private philanthropists. GAVI's support consists of providing

vaccines and strengthening health systems. GAVI funded more than 288 million children (15) in its first decade.

It was created in 2000 and emerged as a response to many countries' difficulties accessing vaccines due to their high prices. The alliance seeks to reduce the cost of vaccines to make them more accessible to developing countries while at the same time ensuring a large sales market for producers, which provides security to both producers and the countries that have access to them.

The partnership uses several means to reduce the price of the vaccines it will acquire; on the one hand, GAVI's orders and purchases on behalf of countries are donor-backed, giving manufacturers some predictability in their production. On the other hand, it pools demand to exploit economies of scale, while companies deal primarily with a single buyer: GAVI procures the purchases through UNICEF Supply Division. This process reduces costs, resulting in even more significant savings (4).

The GAVI partnership aims to support countries with a per capita gross national income (GNI) equal to or less than the US $1,630, an amount adjusted annually for inflation, except for 2021, which was frozen due to the COVID-19 pandemic (16). As part of the model, GAVI-supported countries share vaccine costs, as they pay a small proportion. Because GAVI targets only lower-income countries, it can, in turn, negotiate lower prices with manufacturers.

Subsequently, as countries have increased incomes, they must pay an increasing co-payment until their GNI exceeds the threshold allowed by the partnership and they "graduate." After a transition period following this graduation, countries must assume financing of the total cost of vaccines. That is how GAVI, and its financial backers can finance the poorest countries. Over time, governments with growing economies are called upon to assume greater responsibility and ownership of their countries' vaccination programs.

However, this is a challenge to meeting vaccination targets in many countries. Middle-income countries are home to nearly three-quarters of the world's poorest people and have a birth cohort of more than 100 million children, three times larger than low-income countries. Middle-income countries that are not GAVI-eligible members are diverse, and many face complex immunization challenges (7).

In Latin America, there were initially six GAVI-supported countries. Nevertheless, five of them have been losing support through "graduation"-Bolivia (between 2016-2017), Cuba (in 2016), Guyana (between 2015 and 2016), Honduras (between 2014-2015), and Nicaragua (2018). Therefore, Haiti is the only country in the region that

will continue to be eligible for GAVI support (16). With the loss of GAVI financial support, transition countries must rely primarily on domestic resources to finance immunization services. Thus, these countries must resort to a mixed procurement approach to ensure timely access to an affordable supply of vaccines: on the one hand, they procure Gavi-financed vaccines and, occasionally, other routine vaccines through UNICEF. However, governments must still fund this vaccination (17).

In many of these countries, governments cannot afford to pay the price of vaccines, and private sector prices are unaffordable for most families. As a result, many children living in non-GAVI-eligible middle-income countries cannot access immunization programs, even though some of the interventions of GAVI and alliance partners indirectly support middle-income countries (4).

Finally, other issues related to GAVI show that two-thirds of the voting board members are critical stakeholders in vaccine delivery. One-third of its voting members are independent (or unaffiliated) individuals appointed in their capacity based on their skills and networks. At the same time, low- and middle-income countries are not part of this decision-making forum. Therefore, for many authors, there are conflicts of interest among the members of the decision-making forums and an unbalanced confirmation of the governing structures, which does not contribute to the transparency of their decisions (18).

Thus, the burden of vaccine-preventable diseases is approximately twice as high in middle-income countries as in low-income countries, which are not eligible for GAVI. In addition, the alliance is not exempt from facing financial challenges. In 2010, the GAVI Alliance faced a severe budget shortfall that threatened to limit new vaccine introductions plans. Although it managed to raise sufficient funds to overcome this budget crisis, limitations concerning the long-term stability of subsidies became apparent (8).

2.2 PAHO Revolving Fund

The Revolving Fund was established by the resolution of PAHO's Governing Bodies in 1977 and began operating in 1979 with the purchase of vaccines, syringes, needles, and cold chain equipment. It was created to provide the PAHO Member States with a mechanism to provide an endless flow of vaccines and supplies to implement immunization programs. PAHO does not sell vaccines to its Member States but, on their behalf, establishes annual contracts for the procurement of these biologicals (19).

The Revolving Fund operates in annual cycles where each participating country determines the vaccine needs for the following year. PAHO consolidates the countries' needs, calls for international bidding, and selects suppliers according to WHO and PAHO specifications on vaccine quality, price, and suppliers' track records of timely delivery. PAHO orders the vaccines requested by each country and then monitors those orders, expedites deliveries, and arranges transportation services. Once delivery has been made, PAHO issues the invoice for reimbursement payment, and countries have 60 days to make payment. If the government is in arrears, the entity will not place new orders until payment is made (19).

In this way, the Pan American Health Organization has procured vaccines at low prices by aggregating demand in small and medium-sized countries, achieving a good bargaining position for governments between suppliers. Revolving Fund contracts include a "most favored nation" clause that requires suppliers to give PAHO the lowest price available. However, since most Latin American countries belong to the lower-middle or upper-middle income categories, the requirement that PAHO receives the lowest overall prices has clashed with the tiered pricing strategies of producers, who charge higher prices to middle-income countries (20). All countries purchasing vaccines via the Revolving Fund pay the same price.

Additionally, PAHO includes amongst its Member States, a few low-income countries, like Haiti, with a GNI of only $760, but 70% of its members are middle- or high-income countries with a GNI of more than $4085 and up to $106 000. Since this combination of countries covers an extensive range of GNI and because of the principle, low-income countries, both within and outside the PAHO region, may not get the best possible price (4).

Although one of the benefits of the Revolving Fund is its impact on reducing the cost of vaccines, the introduction of them made with new technologies increased their worth and the countries' need for investment. This situation led some governments in the region to incur debts with the Revolving Fund and jeopardize the sustainability of their immunization programs, which ultimately led to the risk of generating outbreaks of reemerging diseases at the regional level.

2.3 Donations and grants

Contributions and grants for vaccine access come from various sources, such as civil society organizations, non-governmental organizations, philanthropic foundations, corporations, and non-state institutions, with different geographic scopes, subnational, national, regional, and international. More than 73% of the World Health Organization's financing depends on funds provided by voluntary public and private donors, including the Bill & Melinda Gates Foundation (part of the

GAVI Alliance), which is the second-largest contributor (13.5%), immediately after the United States (14.7%) (21).

Some of the complaints about these grants stem from the fact that, while donor countries and their agencies maintain their prominence, UN agencies have lost power and influence, absorbed by broader agendas defined by a set of new institutional actors, including significant funds such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Global Alliance for Vaccines and Immunization (GAVI), the Global Health Initiatives, the Bill and Melinda Gates Foundation (among several philanthropic organizations) and many non-governmental organizations (21).

This has shaped new dynamics of international cooperation related to the increasing diversification and interference of private actors in the public sphere. Another difficulty associated with donations is that, while international funds have been significant in promoting immunization systems against some specific diseases, they are not sufficient and do not guarantee the long-term sustainability of vaccination programs in the countries (2).

Some authors consider that pharmaceutical companies must also respond to access vaccines (2). They have been doing it. After recovering their investments in research and development sales in wealthy nations, these companies have provided many vaccines at a reduced cost to low- and middle-income countries, such as poliovirus, hepatitis B, and pneumococcal disease. However, this delays the introduction of new vaccines to countries that cannot afford them in the first place (22). In addition to this, there is a significant problem of lack of research and financing for the development of vaccines for diseases that only affect middle and low-income countries since there is no market where they can recover their initial investment, which involves their generation.

3. Innovative practices for the sustainability of immunization programs.

3.1 Tools to assist in economic analysis of new vaccines

All decisions regarding the introduction of a vaccine in a country should include an analysis of the country's ability to bear the costs of the vaccine and associated operating expenses in the short and long term. The budget impact analysis should estimate the costs of adding the new vaccine and its budgetary implications over time (10). Although these decisions are not in themselves direct methods of financing, they are vital tools for predicting, in some way, the sustainability of immunization programs over time by determining the cost-effectiveness of these programs.

For this purpose, some models have emerged to estimate the costs of including new vaccines. From this, a new vaccine can be considered affordable if its introduction can be financed by the immunization budget of each country in the medium and long term, without significantly affecting the resources available for other vaccines or other public health priorities.

These models should include an analysis of the cost of co-financing the portion of vaccine doses from countries supported by GAVI or other entities. It should also have all supplies necessary for vaccine delivery to be effective and for changes required in the immunization program (10). In this way, long-term sustainability can be predicted based on standardized models. New vaccines are not introduced due to the risk of discontinuing production over time or undermining funding for other health programs.

One model used to perform these analyses is the ProVac model (TRIVAC/CERVIVAC), employed to calculate the cost-effectiveness of new vaccines. This tool created by PAHO can estimate the costs of specific vaccines and the cost-effectiveness ratio of vaccination. The device produces graphs showing the incidence of diseases and deaths, with and without vaccination. It calculates the cost savings per treatment, the cost per disability-adjusted life years (DALYs) averted, and other cost-effectiveness ratios (23).

In addition, there is the "OneHealth Tool," developed through the International Health Partnership (IHP+), which provides a framework for planning, costing, impact analysis, budgeting, and financing of health strategies in countries, focusing on integrated planning and health systems strengthening. The primary purpose of this tool is to assess the health investment needs of low- and middle-income countries. The tool can calculate the cost of specific interventions and health system components (10).

In the same vein, the tool "Immunization costing and financing: A tool and user guide for comprehensive Multi-Year Planning" enables countries to estimate the costs and financing needs of their immunization program to meet their objectives in the coming years, including the addition of new vaccines and other activities, as well as bridging the financing gap (10).

The tool "Making choices in health: the WHO guide to cost-effective analysis" presents the WHO-CHOICE methodology for performing a "generalized cost-effectiveness analysis." It allows decision-making and priority setting at the national level by comparing the cost-effectiveness of new vaccines with other public health interventions (10).

The evidence provided by these tools and models allows immunization programs to make evidence-based decisions, budget for current services, plan for introducing new vaccines, and evaluate the efficiency of service delivery strategies. In addition, the evidence collected on immunization costs is also helpful for presentation to national governments and international funders, enabling them to make decisions on the allocation of priority resources.

While many of these tools have support groups to develop analyses, ultimately, the study developed must be owned by each country so that it understands its limitations, correctly interprets the data, and makes better-informed decisions that lead to long-term results on the sustainability of its immunization programs (23).

3.2 Differentiated or tiered prices

This strategy is quite simple: to make countries pay prices according to their ability to pay, determined by their varying level of national income. That is how buyers are charged different fees for the same product. In the specific case of vaccines, low-income countries are charged a reduced price for vaccines (24) compared to the open market rate charged through the bulk purchasing systems established by UNICEF and PAHO. To some extent, tiered prices already exist for vaccines, with GAVI countries paying the lowest price and non-GAVI lower-middle-income and lower-middle-income countries delivering a middle level (4).

The most used approach to tiered pricing is to segment the public and private sectors with lower prices for government-provided medicines. Another method proposed to achieve domestic market segmentation is to charge higher prices in the insured market while offering lower prices for all other sectors, including the public, private, and nonprofit sectors. Thus, tiered pricing has been proposed as an alternative to high costs when there are separable high- and low-middle-income markets and when the seller exercises significant pricing power, such as when there is limited or no competition due to patent protection, data exclusivity, or other barriers to entry into the vaccine market (20).

Tiered pricing benefits consumers in the low-price market and producers, given the prevailing cost structure of vaccine production, as high-volume vaccine production leads to lower manufacturing costs, which helps even consumers in the high-price market. This decrease in prices is due, in part, to the fact that the yield per batch increases as experience is accumulated in the production processes, and marginal costs tend to decrease over time and with the increase in volume. However, it must be considered that there is a variation in the production of different vaccines (24).

However, because GNI growth does not always represent a country's investment in social development and local risk situations may vary, criteria in addition to GNI could be used to rank countries, such as the burden of disease, and immunization coverage, among others. In addition, this approach could include bands within price levels based on factors such as volumes ordered and certainty of demand. Of course, public markets should be treated differently from private markets.

Tiered pricing would help assist countries graduating from the GAVI model. The development of technically challenging products and the high fixed costs associated with them contribute to high barriers to entry, as in the case of new vaccines involving novel technologies. Maintaining more than three or four manufacturers for many vaccines is difficult, limiting competition, which would generally be a compelling incentive to reduce prices. Therefore, while tiered pricing could be applied to all GAVI vaccines, it would be crucial for new vaccines with few manufacturers (4).

A fundamental weakness raised concerning the tiered pricing strategy is the reliance on GNI per capita levels, as many middle-income countries have very high levels of inequality. Therefore, tiered prices may be available to the upper or middle classes in a country but not to the poor in that same country (20). Also, tiered pricing becomes impossible when the high-price market disappears, and manufacturing is not considered profitable (24).

Because of this, some general shortcomings of tiered pricing have been documented, including its inferiority in the face of genuine competition, arbitrary divisions between populations, and the lack of pricing transparency that can result. Prices should be set relatively that reward innovation and ensure that cash-strapped health systems can ultimately afford products beyond donor support (20).

3.3 Patent-related aspects

The economic theory of patent protection holds that innovation occurs because patents protect the research and development investment made by the innovator. Proponents of this theory claim that, without patents, innovation in drugs and vaccines would occur at a significantly slower rate. For this theory, a patent incentivizes innovation by providing the innovator with a temporary monopoly over his creation and protecting him from the threat posed by imitators who wish to make a cheap replica of the product. However, due to complex regulations and standards for the generation of many new vaccines, manufacturers run little risk of having generic imitations (25).

Additionally, for proponents of this theory, if generic vaccine manufacturers have the exact production costs as innovators but none of the upfront product development costs, copycats could sell the copycat product at significantly lower prices than the innovator product. Therefore, potential investors would not finance the development of the innovative products, as they know that they would not recoup their initial investment, leading to a stagnation of research and development, which would halt the progress of modern medicine, which is why the theory is widely accepted (25).

On the other hand, it has been argued that patents can negatively affect the acquisition of many vaccines since patents grant a temporary monopoly to the patent holder. Thus, preventing generic entry into the market increases competition among pharmaceutical manufacturers and drives down product prices (25). Additionally, there is the problem that patents provide a property right over the knowledge generated by an invention. In purely economic terms, knowledge is a public good, an intangible asset that anyone can consume to the extent desired without diminishing the amount available to others.

Therefore, some authors have proposed the need for companies to waive the patent rights to vaccines for developing countries as a mechanism to achieve affordability. However, this still represents a problem for vaccines for diseases that are more prevalent in emerging countries since the market would not be sufficiently attractive to achieve this competition, and many countries that have diminished scientific and technological production capacity may be left behind with each introduction of innovative vaccines (3).

On the other hand, the alternative of generating a compulsory license has been proposed, whereby the patent owner is obliged to grant a license to another company, allowing that other company to manufacture a generic equivalent of the biological product through a governmental decision. This generic equivalent can then be distributed under a different brand name and usually at a much lower price than the patent owner's (26).

However, this tool has been used effectively by countries with domestic manufacturing capacity. However, in countries that do not have domestic manufacturing capacity, compulsory licenses are less effective in ensuring lower prices (26). In this sense, patent liberalization would have to go hand in hand with technology transfer, an aspect that will be addressed in the next chapter.

Finally, patent pools consist of licensing contracts between two or more parties. The interested entities control a group of patents on elements necessary to produce a given vaccine that could be used. Pharmaceutical companies could create a pool with the patents required by each of the companies involved to develop a new drug

or grant a generic company license without paying royalties. The importance of this type of collaboration is that it can represent a contractual alternative to include competitors with dependent or complementary technologies. The latter makes it possible to reduce transaction costs and prices of the final products, thereby promoting society's access to such innovations (27).

3.4 Technology Transfer

A critical factor in achieving the financial sustainability of immunization programs is operational self-sufficiency when a country purchases or produces all the vaccines it ordinarily requires (19). Many pharmaceutical companies are already actively involved in technology transfer to vaccine manufacturers in developing countries.

The pharmaceutical industry has identified eight conditions as necessary for successful technology transfer relationships: a viable and accessible domestic market, political stability and sound economic governance, clear economic development priorities, adherence to high regulatory standards, availability of skilled workers, adequate capital markets, strong and effective intellectual property protection and enforcement mechanisms, and a good relationship between industry and government, as well as the ability to collaborate effectively over long periods (8).

However, most low- and middle-income countries do not meet these requirements and would not be candidates for access to vaccines through technology transfer. Therefore, to have this mechanism of sustainable access to immunization, in that case, countries must increase their scientific and technical capacity. Likewise, Governments ought to commit to improving and strengthening those political and financial aspects guaranteeing the national laboratories' participation in the sustainable supply of vaccines to vaccination programs and the research, development, and production of new vaccines (1).

Again, this represents a problem for introducing vaccines for diseases of higher prevalence in emerging countries since the market would not be sufficiently attractive to achieve this competition. Many countries with diminished scientific and technological production capacity may fall behind when introducing innovative vaccines (3).

3.5 Public-private partnerships

Public-private partnerships have already been working to support the sustainability of some countries' immunization programs, such as the GAVI Alliance. However,

new partnership models are needed to ensure a wider number of countries sustainably access vaccines.

It has been postulated that countries can mobilize new resources by increasing national or local funds and obtaining support from new donors or loans from development banks. Several countries have used funds released through debt relief for heavily indebted emerging countries or as part of poverty reduction strategies (28).

Other countries have been prosperous in increasing donor and government financial commitment by establishing sector-wide approaches to pool government donor funds to help the country implement its immunization program. Several international partners, including the GAVI Alliance and the World Bank, encourage countries to develop health systems financing platforms to pool funds from donors to strengthen the health system to support national health plans (29).

Some countries have found innovative ways to finance immunization, including setting aside funds from national lotteries, establishing a national health fund, or creating taxes for luxury items or products harmful to health, such as tobacco and alcohol (29). However, governments must demonstrate a long-term commitment to financing the immunization program and regularly increase that commitment over time. Strategies should articulate an increased allocation in the Ministry of Health budget for the immunization program (which has been shown to increase the government's budget) and obtain long-term donor commitments (30).

On the other hand, civil society organizations can also articulate each other to play a crucial role in expanding access to immunization. In addition to contributing to the delivery of immunization services, they can help improve access to communities in unstable socio-political situations and hard-to-reach communities. They can also play a key role in local and national advocacy and hold governments and service delivery partners accountable, which together help to provide immunization programs with greater sustainability over time (30).

In addition, there must be coordination between the government and the pharmaceutical industry through balanced and intelligent negotiations that do not neglect incentives for innovation and research (3). In this same sense, the articulation between the industry and university and research centers can generate the technology transfer necessary for countries to produce their vaccines, which would cause long-term sustainability of their immunization programs. For this, the articulation should include training models for human talent to achieve the empowerment of each country.

However, some authors have suggested that many public-private partnerships are often not functional and do not fulfill their explicit objectives. They also point out that if participation is hindered by the resistance of some actors or the inability of others to install their demands, the public-private articulation schemes formed can only serve limited objectives (3).

Therefore, new forms of regulation are also required, both in terms of norms and public-private articulation mechanisms. Each organization's role in developing and sustainability of immunization programs is clear, and the agreed commitment is somehow guaranteed overtime.

3.6 Payment systems

Some alternatives have been proposed for accessing new vaccines, which is a fundamental component of the sustainability of vaccination programs. If mechanisms do not get incorporated for accessing new vaccines, which involve increasingly higher costs, immunization programs may not be in force over time. One proposed alternative is to establish cost-recovery pricing, whereby private companies develop vaccines and are rewarded with patent rights. However, the government or private insurers analyze the cost of development and production to set a maximum price when incorporating the vaccine. However, there is a risk of overpricing, which jeopardizes the affordability of immunization (31).

On the other hand, cost-recovery pricing gets established. Thus, a vaccine is priced at the necessary level to return to the manufacturer an amount that would cover the total costs accrued for development and production. This approach can contemplate two paths: 1) cost-of-production pricing, in which the prices are set to compensate the manufacturer only for manufacturing and distribution costs, and 2) cost-of-development and product pricing, in which the price fully recovers the manufacturer's costs for all the research and development effort that ultimately produced the new treatments, as well as the costs necessary for manufacturing and distribution.

Value-based pricing is the method used to determine a maximum price for a vaccine based on cost-effectiveness and cost-effectiveness analysis. It provides a recommended total price in proportion to a new vaccine's added health and economic benefits. The price scale concerning the benefits of the intervention is set to provide the highest price where the benefits could receive compensation without an increase in cost (31).

Some monetary incentives are generated by private organizations, such as the Bill and Melinda Gates Foundation, in collaboration with various national governments

that have used it to stimulate the development and dissemination of a vaccine against pneumococcal disease. In addition, there are approaches to incentivize private companies to develop vaccines, such as awarding a monetary prize to companies that produce vaccines in exchange for intellectual property. The incentive need not necessarily be a fixed amount but could be scaled based on the total number of people treated. Once the government has paid the incentive, its ownership would allow it to separately contract for the production and distribution of the vaccine without the need to distribute future revenues from the product's sale.

Finally, advanced market commitments (AMCs) can be generated, designed to incentivize the development of novel new vaccines, often for underserved populations, by subsidizing research and development costs through the funder's commitment to pay a purchase price in the future if development is booming. The funder, a government or group of governments, or donors, can guarantee payment for a successful product, thus eliminating the uncertainty a manufacturer faces when innovating with vaccines. Subscription models work similarly, with funders and manufacturers agreeing on the price of a vaccine in a way that guarantees a minimum return on investment and a cap on total costs, regardless of the number of vaccines needed (31).

3.7 Healthy taxation

“Healthy" taxes are levied on unhealthy products such as tobacco, alcohol, and sugar-sweetened beverages. The consumption of these products is a significant risk factor for multiple non-communicable diseases, including cardiovascular diseases, cancer, respiratory diseases, and diabetes, and their taxation can represent an essential source of revenue for the health system, which can be used, among other things, to finance new vaccines in the countries of the region, especially when the Latin American and Caribbean region is reported to be one of the areas with the highest consumption of sugar-sweetened beverages and high alcohol consumption. As reported in the literature, creating new revenues through tax collection, and contributing resources to the system are positively correlated with better health indicators. On the other hand, it has been shown that this type of healthy tax and others such as those contributed by national lotteries create a "fiscal space" and generate additional immediate tax revenues that can address the problems of access to vaccines, and that, in some way, would guarantee their sustainability over time (32).

In this regard, PAHO produced a regional study on the fiscal space for health, which analyzed the experiences of 14 countries in the Region. The results show that governments can successfully generate new resources for health to reach the GDP threshold recommended for universal health; furthermore, it is recommended that these resources be mobilized from domestic sources. A specific recommendation is

to add new or increase existing taxes, especially on harmful products to health, improve the efficiency of health systems and public health spending, and improve tax administration (33). From this recommended GDP could emerge programs to enable access to vaccines in the countries of the Region.

3.8 Tax benefits, soft loans, and strengthening of vaccine legislation

Given the complexity of the logistics chain surrounding the manufacture, transit, storage, and distribution of vaccines, trade facilitation, improvement of customs procedures, and simplification of procedures are urgently needed as a fundamental component of sustainable access to vaccines to gain access to them in the region. To guarantee the supply of the internal demand of the countries where vaccines are produced and the raw materials and auxiliary products for their production, governments impose restrictions on exports, as seen in the case of the COVID-19 vaccine. Tariff barriers to raw materials and additional products for vaccines should be eliminated, thus reducing transaction costs.

Therefore, some incentives to achieve equitable and sustainable access to vaccines in the region are eliminating tariffs on raw materials, auxiliary components, and the drug itself and eliminating all other restrictions on trade of these products (both imports and exports). Thus, this will substantially reduce vaccine prices, especially considering that most ancillary products such as vials, syringes, and adjuvants are produced in Europe and the United States (34). In addition, exemptions from payment of internal taxes can be generated in each country to sell vaccines and the inputs necessary to produce them.

The above must be supported by legislative components that can secure resources for vaccination programs, including a budget line item for vaccine purchases; regulations to ensure timely and reliable disbursement of resources; tax exemptions for vaccines and immunization supplies; the flexibility to sign contracts with suppliers; and simplified customs regulations to speed up the import process and reduce transaction costs, some of which were mentioned above. This legislation has shown that those countries can secure a budget line for vaccines and other expenses of the vaccination program, thus ensuring its sustainability.

Another mechanism that can be implemented consists of long-term, low-interest loans, or so-called "soft loans," enabling low- and middle-income countries to avoid falling behind in access to vaccination. In addition, the funds raised with these loans can be used not only to purchase vaccines but also to acquire raw materials, personnel training, and technology transfer, which would enable countries to ensure the self-sustainability of their vaccination programs in the future (35).

3.9 Country consortia

The existence of alliances that provide political and technical mechanisms is essential to address the region's public health problems, including access to vaccination. Thanks to these alliances, it is possible, in the first instance, to exchange epidemiological data and to search for information for the diagnosis, surveillance, control, and prevention of immunopreventable diseases.

On the other hand, creating regional networks could generate incentives for research, technological innovation, and vaccine production. In this way, when integrating efforts, economies of scale and the individual capacities of the countries can be promoted through cooperation to adopt mechanisms for the negotiation and joint purchase of vaccines, which would reduce vaccine prices and ensure demand for producers.

Finally, regional funds could be set up to provide financial support for the acquisition of vaccines and to mobilize existing regional networks to organize shared research, human resources training, and technical assistance-cooperation for vaccine development (36).

4. ANALYSIS AND DISCUSSION OF THE TOPIC

Although there are numerous obstacles to the financial sustainability of immunization programs, in low- and middle-income countries, there is a consensus that a felt issue is that of pricing and achieving economic sustainability. In addition, the costs of immunization programs are increasingly high due to emerging innovative vaccines and maintaining all those already incorporated. Today, the primary way in which the sustainability of immunization programs in low-income countries is met today is through the GAVI Alliance. However, many middle- and low-income countries that do not qualify for GAVI funding have difficulty financing new vaccines without assistance (12).

An example of the difficulties that low- and middle-income countries face in acquiring vaccines was experienced in the aftermath of the COVID-19 pandemic and the race to acquire the vaccine. The COVID 19 Global Access to Vaccines (COVAX) mechanism was a global multilateral collaborative initiative to accelerate the development, production, and equitable access to COVID-19 vaccines. The PAHO Revolving Fund worked directly with COVAX to ensure equitable access to the COVID-19 vaccine for countries in the Region (37).

However, the mechanism did not work as it should have. Residents of wealthy and middle-income countries initially received about 90% of the nearly 400 million vaccines delivered. According to projections, many other nations would have to wait years for the complete vaccination of their populations (38). The situation, in a way, reproduces the current global system: the wealthiest countries buy the most vaccines. In contrast, the poorest countries will not have doses to administer even to their most vulnerable populations. As a result, nearly 90% of the inhabitants in almost 70 low-income countries were less likely to be vaccinated against COVID-19 in 2021. Meanwhile, other nations initially purchased enough doses to vaccinate their populations five times over (39). Thus, middle- and low-income countries could not make large-volume purchases or buy vaccines when the risk of failure was still very high, so they did not gain priority access.

On the other hand, one of the main limitations of the GAVI partnership is that it fails to establish mechanisms to ensure sustainable vaccine pricing once the initial period is over and the country has graduated from partnership support. Therefore, a way is needed to ensure that the population not living in GAVI-eligible countries also has access to sustainable immunization programs and ultimately has the right to a healthy and productive life. For GAVI-eligible countries, as their incomes increase, a way must be found to ensure the continuity of their gains in immunization coverage when they graduate from GAVI support due to unsustainable prices. Instead, the Pan American Health Organization's Revolving Fund succeeds in reducing costs through bulk purchasing systems but has not been sufficient to ensure affordable and sustainable prices for new vaccines.

The presence of multiple vaccine manufacturers from developing countries is vital in generating sustainable vaccine prices. It is now widely recognized that the emergence of generic drugs or, more importantly, the entry into the market of multiple generic suppliers is the best mechanism for rapidly achieving price reductions. However, there is a need for strategies whereby countries can access the technology and know-how to manufacture their vaccines and generate true long-term sustainability of their immunization systems, as there are markets that would not be sufficiently attractive. Many countries that have diminished scientific and technological production capacity may be left behind with each introduction of innovative vaccines (3).

Additionally, tiered pricing methods have emerged as another efficient alternative, but in some cases have had mixed results and have not consistently resulted in sustainable prices, particularly in the case of new vaccines. It is necessary to generate tiered pricing considering factors in addition to GNI, such as disease burden, expected demand for vaccines, and even to generate additional segmentation within countries, considering the inequalities present in the countries in the region.

Some authors have concluded that future strategies to improve access to new vaccines will need to 1) simplify regulatory pathways for biosimilar vaccines, 2) address intellectual property barriers, and 3) reduce barriers and timelines for entry of multiple new suppliers through technology and know-how transfer. In this regard, the strategy of patent management should be recognized in the case of the entire market for vaccines for diseases specific to low- and middle-income countries (8).

On the other hand, it is necessary to generate public-private articulations to access financing funds with long-term commitments. For this, the countries must have a foreseen demand and precise cost-effectiveness analyses, which allow mitigating the uncertainty of the financiers and reducing the excess costs of the immunization programs. It could generate Centralized purchases, giving each country a price under its ability to pay. Vaccine manufacturing companies can access larger markets and increase production volumes, ultimately reducing manufacturing costs (4).

For this, it is necessary to generate a space in which each country that requires the financing process can establish the expected demand for each vaccine based on its real needs and provide some guidance on the desired product profiles, which would generate a better basis for decision-making on vaccine development and planning, thus reducing the risks associated with the development and distribution of vaccines. This information is also critical for getting suppliers and development partners to generate safer strategies and plans (9).

In the past, subsidies, and grants funded much of the immunization systems in low- and lower-middle-income countries. This model of health care is now outmoded as it precludes long-term sustainability. On the other hand, the world's poor and the burden of disease are no longer concentrated in low-income countries but are now primarily in middle-income countries. As they transition out of funding for healthcare, they face significantly higher prices for health products than those received by global health mechanisms.

As donor aid (particularly GAVI in Latin America) declines and government expenditures do not increase fast enough, families assume most health expenditures in low- and middle-income countries, which pose a significant risk to sustaining immunization gains. For some transition countries, high vaccine prices may jeopardize the financial sustainability of the health sector budget (40). In addition, the COVID-19 health emergency has temporarily shifted priorities. It is likely to continue for some time, necessarily impacting the financing of countries' ministries of health and causing resources to be reallocated, often leaving aside fundamental components of promotion and prevention, such as immunization programs.

In addition, achieving sustainability of immunization programs in the region also requires demand forecasting and joint procurement. However, it must also include collaboration between agencies and governments to negotiate effectively with manufacturers and investment to expand the manufacturing base, promoting competition. Funding agencies and other stakeholders can play a crucial role, but it is vital that governments, including major emerging economies, are the drivers of effectiveness to ensure long-term sustainability (41).

Finally, it is essential to access other innovative practices that have proven successful in other regions, such as opening a fiscal space and adding taxes to products harmful to health or national lotteries aimed at the financial sustainability of vaccination programs. In addition to these strategies, providing tax and tariff benefits with strengthened legislation in this area might promptly guarantee the outlay of these resources. Those tax exemptions would be granted for vaccines, associated inputs, and more lax customs processes, reducing transaction costs in the vaccine market. Similarly, generating alliances between countries in the region to join efforts to promote economies of scale, have common financing funds, and establish the adoption of mechanisms for negotiation and joint purchase of vaccines, would impact their price and, finally, their long-term sustainability.

5. SUGGESTED RECOMMENDATIONS

- Vaccine financing and sustainability cannot be discussed purely about access to vaccines. The capacity of countries and regions to develop research and development processes, carry out operational processes and evaluate immunization programs must be considered, including the training of human resources in low- and middle-income countries.

- Country-specific data should be generated, and multilateral collaboration in basic science and vaccine development should be encouraged, reinforced by peer-to-peer training and cross-country exchanges. Increased networking among research centers can facilitate the exchange of ideas. It will efficiently generate partnerships among institutions in high, middle, and low-income countries to enable sustainable and sustained access to new vaccines and technology transfer. Similarly, changes in technology or immunization service delivery strategy can reduce average costs as efficiencies are gained.

- Data on the costs and benefits of introducing a new vaccine is needed to support sustainable and rational decisions on vaccine adoption and subsequent planning for a new vaccine once a decision has been made.

- One of the advantages of the tiered pricing alternative can be to structure groups of price levels based on country income (using, for example, World Bank income groupings), given that GNI growth does not always represent the country's investment in social development and local risk situations may vary; besides, price levels can include additional criteria such as disease burden to be immunized, immunization coverage, the volume of demand, with differentiation between public and private markets (4).

- It is necessary to establish an expected demand for each country and plan the production accompanied by joint purchasing to achieve the lowest possible prices within the existing escalation levels (6).

- By giving countries prices for vaccines that reflect their ability to pay, they can make better programmatic and financial planning for purchasing these vaccines. In return, vaccine manufacturers can access larger markets with anticipated demand, increase their production volume, and thus reduce manufacturing costs (4).

- Decision support for introducing new vaccines in low- and middle-income countries is essential to maximize the efficiency and impact of vaccination programs. It requires global technical cooperation and the establishment of public-private partnerships with long-term commitments.

- It is necessary to combine fiscal, tariff, and tax strategies for products that are harmful to health to promote the entry of new vaccines at a lower cost, supported by regional alliances between countries.

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