MA@PoC
eISSN 2399-2026

Med Access @ Point Care 2017; 1(1): e10-e15
DOI: 10.5301/maapoc.0000004

REVIEW

Open Access

Access to oncology drugs in Brazil: juggling innovation and sustainability in developing countries

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ABSTRACT

Brazil is a developing country of continental proportions and faces challenges in organizing an effective, universal, and affordable public health system. In a context of limited resources, the budget allocation to health care must be consistent with the health priorities of each population. The Brazilian population is ageing and the number of new cancer cases is likely to steadily increase in the near future. To deal with the extra cancer burden, strategies to match this future health necessity must be proactively put in place.

Keeping the balance between the incorporation of a new drug and the sustainability of the public health system is a complex matter. Decisions for incorporation must be assessed, taking into consideration the ability of the drug to improve the public health in relation to its monetary impact. This is a societal discussion, and multiple stakeholders are involved in this process – from health authorities to pharmaceutical companies, researchers, and civil society.

This article discusses the issues of incorporating a drug into the public health system and the strategies to improve access to innovative medicines, from the regulatory to the drug development perspectives.

Keywords: Affordability, Brazil, Cancer drugs, Health innovation, Oncology drugs, Sustainability

Brazil: a continental country with huge inequalities

Brazil is the largest country in South America and is formed by a mix of people from all around the globe. Its heterogeneous and mixed population is reflected in regional habits, food, and folklore. Brazil became independent from Portugal in 1822, and has been a Federative Republic since 1889. It is considered a developing country and until 2010 it was one of the world's fastest growing major economies. Since then, the country entered a recession. As at 2015, Brazil was the ninth world economy (1).

Brazil's diversity, seen in its landscape, its people, and its habits, is, unfortunately, also seen in wealth distribution. It is a country with huge social inequalities (2). Despite the decline in poverty levels, in recent decades (3) inequalities in income distribution still have been inconsistent with the size of its economy (2).

Accepted: January 5, 2017
Published online: January 20, 2017

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Unfortunately, Brazil's inequalities are also seen in the public's access to health care. The Brazilian public health system (SUS – Sistema Único de Saúde) was created with the new Brazilian constitution of 1988 (4), with the purpose to deliver equal, universal, and integral health care to all Brazilian citizens. The public health system is supposed to be organized in a decentralized manner, to locally adapt to the specific health problems of each region from the tropical diseases of the Amazon forest to the pollution-related diseases of its megalopolis. However, it is underfunded, spending around US$150 per patient per year (5, 6). Table I shows the median health expenditure per capita per year in Brazilian metropolitan regions. It is not yet organized or hierarchized to promote its objective and deal with the real-life health problems of its citizens (7).

Nontransmissible chronic diseases in Brazil

Currently, worldwide, nontransmissible chronic diseases (NTCD) are the major cause of death, accounting for 36 million deaths per year. This group of diseases is composed of cardiovascular diseases, diabetes, lung diseases, and cancer. It has been estimated that 80% of the deaths by NTCD have occurred in middle- and low-income countries. As a convention, deaths caused by these diseases in people under the age of 60 are considered to be premature, as they may reflect the lack of proper health assistance. When comparing NTCD premature deaths, 13% occurred in developed countries, whereas 29% occurred in developing countries.

TABLE I - Median health expenditure per capita per year by Brazilian metropolitan regions

Metropolitan city	Median expenditure per capita per year (US$)	Hospital beds per 800 people	Tuberculosis incidence by 100,000 people
Belo Horizonte-MG	283	2.15	28.42
Campo Grande-MS	279	1.75	33.78
Teresina-PI	265	2.46	33.19
Goiânia-GO	236	2.22	18.43
Porto Alegre-RS	220	3.27	104.59
Cuiabá-MT	214	2.09	76.39
Aracajú-SE	211	2.65	34.85
Vitória-ES	210	3.57	50.52
João Pessoa-PB	204	2.74	45.14
Curitiba-PR	202	1.76	22.49
São Paulo-SP	176	1.26	54.6
São Luís-MA	170	2.86	62.29
Rio de Janeiro-RJ	170	1.63	86.73
Fortaleza-CE	166	1.98	65.25
Florianópolis-SC	152	2.62	48.67
Maceió-AL	145	2.37	50.89
Palmas-TO	143	1.71	16.57
Natal-RN	141	2.48	47.85
Recife-PE	136	3.8	90.07
Porto Velho-RO	126	2.47	67.93
Manaus-AM	95	1.33	84.96
Salvador-BA	93	1.92	65.93
Belém-PA	86	1.65	105.13
Boa Vista-RR	82	1.75	29.57
Rio Branco-AC	73	1.89	68.65
Medium expenditure	164		

In Brazil, this figure is similar to that of developed countries, with the reduction of deaths from infectious diseases and the increase of NTCD. As at 2011, 72% of the deaths in Brazil were caused by NTCD (8). Brazil has committed to the global effort to control NTCD, following the World Health Organization (WHO) meeting of 2011, by implementing the "Strategical plan of action to face the non-transmissible chronic diseases 2011-2022 (Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas Não Transmissíveis (DCNT) no Brasil, 2011-2022)" (9).

After the first observation period, between 2000 and 2011, mortality declined in all of the four disease groups: 3.3% in cardiovascular diseases, 4.4% in chronic respiratory diseases, 1.7% in diabetes, and 0.9% (the lowest reduction) in cancer (10).

The worse result in reducing cancer mortality is likely to be multifactorial. A number of variables can be implicated as factors related to the complexity of the oncological diseases and the inherent variety of treatments, and, most importantly, factors related to access to proper health care, which includes the availability of modern and effective treatments.

New treatments, new costs

In recent years, there have been many advances in oncology drug development. The deeper understanding of tumor biology and immunology has allowed the development of target drugs to specific tumor aberrations (11), as seen with the tyrosine kinase drugs against lung cancer (12, 13), and, more recently, the revolution of immuno-oncology drugs in multiple diseases (14, 15).

Nevertheless, these improvements in treatment come at a cost with some of these treatments ranging from tens of thousands (16) to more than a million dollars per patient per

year of treatment (15). Drug costs account for around 15% of the total cost of oncologic patients (17), yet a European study evaluated that this cost has risen over time, from €4.3 to €26.3 per capita. This figure is slightly higher than the increase in the overall cost of cancer care (18).

Cancer is a major public health issue with almost 14 million new cases diagnosed each year (19). These numbers are likely to increase because of environmental factors, demographic changes, and population ageing (20). In 2000, there was an estimated 400 million people over the age of 60. By the year 2050 this number is expected to be 1.5 billion people; 20% of the world's population (21).

Cancer burden in Brazil

The Brazilian population is also ageing fast. In the 1960s, the percentage of people over the age of 60 was 4.1% of the total population. By 2025, this figure is predicted to go up to 15% (22).

In 2012, Brazil had around 430,000 cancer diagnoses. As with other countries, this figure is likely to increase steadily with the predicted Brazilian population ageing, and proactive measures to deal with the future cancer burden are urgently needed.

From its population of 200 million, 160 million are covered by the public health system (the SUS). Parallel to the SUS, Brazil has a private health system that works completely independently, and is organized similarly to the North American "fee-for-service" health system (23).

In the SUS, access to innovative and high-cost drugs is low, and, in general, it is lagging many years behind in relation to the date of drug approval in developed countries. For example, trastuzumab was approved in the USA in 1998 (24), but was only available and reimbursed by the SUS in 2012, although only in the adjuvant setting (25). Around 20% of the Brazilian population can afford private health insurance and may have access to some modern cancer drugs.

Approval, pricing, and reimbursement: a lengthy process

The process for the incorporation of drugs in the Brazilian Public Health System is similar to that of most European countries (26). For a drug to enter the Brazilian market, its safety and efficacy have to be evaluated by the Brazilian Health Authority, ANVISA (Agência Nacional de Vigilância Sanitária). Pricing and reimbursement decisions are made in a second stage, when the approved drugs are appraised by the Health Ministry.

Brazil has its own health technology assessment (HTA) body, the CONITEC (Comissão Nacional de Incorporação de Tecnologia), which is responsible for making the appraisal of approved drugs and other health technologies and providing guidance to the Health Ministry. It has the responsibility to make recommendations for their incorporation – or not – in the public health system. As with other HTA agencies, such as the UK's National Institute for Health and Care Excellence (NICE), it has a specific and clear procedure for the submission of each drug's dossier. It must include a systematic review of the proposed technology along with pharmacoeconomic studies. Nonetheless, the decision-making process is not completely clear, and, in some cases, conflicting and divergent recommendations occur between two deliberative meetings.

Reimbursement decisions are taken based on the expected societal benefit of an intervention in relation to its cost, and many approaches are used to measure it. Health gains can be appraised in relation to the drug's monetary value, which is normally evaluated as money per quality-adjusted life year (QALY: a product of the quality and the quantity of life gained with a given intervention) (27). These analyses are context-sensitive, meaning that different countries can embrace distinct health policies and reimbursement decisions using similar results. The UK's NICE is among the HTA agencies that support the use of QALY in health policy decision making. NICE considers cost-effective interventions costing between £18,000 and £40,000 per QALY (28). In the Netherlands, this value is around €18,000 (29). In the USA, the use of QALY has been prohibited by the Patient Protection and Affordable Care Act 2010 (30). The WHO proposes that interventions costing less than three times the gross domestic product per capita for each disability-adjusted life year (DALY: the sum of years living with disability with years of life lost) saved should be considered as cost effective (29), but no formal recommendations exist. At the end of the day, the investment of public resources is a societal decision that must be democratically discussed by all stakeholders.

The UK's NICE, for instance, has recommended against the reimbursement of drugs in the public health system, despite its clinical benefits: "The resources to be invested in this technology are disproportional to the health benefits it provides." This is the case with pertuzumab and TDM1; despite the positive results in phase 3 studies, NICE have recommended against their reimbursement by the National Health Service (NHS) because they consider their benefits to be disproportional to their monetary value (31, 32). In Brazil, these analyses – and the exact criteria used to draw conclusions about the recommendations – are sometimes not so clear. Some of the conclusions state that the technology is not "good enough," or that "the results are not robust enough," or that "there are a range of alternative drugs already available in the public health system" (33, 34).

These recommendations were made despite the international HTA's recommendations to the contrary. This causes mistrust between physicians, medical professional societies, and health authorities. One of the criticisms is that high-cost medications are evaluated as "not effective," or with "low effectiveness," to avoid societal pressure for their reimbursement. Critics also state that a preferable evaluation would be as in the UK: recognizing the effectiveness of the technology and discussing with civil society the budget allocation priorities, according to and adapted to the real-life problems of the Brazilian people.

Dealing with the increasing costs and the bureaucracy barriers

Cost-effectiveness analyses are, as the name suggests, an evaluation of the health impact a technology brings to the daily clinical practice in relation to its monetary value. This

analysis is context sensitive as it depends on the country's resources and health budget. It is also dependent on the relevance of a given public health problem and the possible improvement that a technology can produce to solve that issue. A sustainable and effective health system must deal with the delicate balance between all of these variables.

What are some of the solutions that could be implemented now?

Looking at the cost-effectiveness equation, it is easy to recognize that by increasing the health budget, the weight of "cost" is diminished. It is more likely that countries that spend more on health care adopt new health technologies earlier (35). Also, as a country increases its expenditure in health, it is more likely that drugs are reimbursed earlier and are used in larger quantities. However, increasing the health budget is a subject that involves the country's development level and economic situation. The issue of a country's economic development and income goes far beyond that and is a lot more complex than the pure evaluation of the equation health technology costs versus results (36). Thus, relying on improvements in the economic conditions and increases in the health budget can be a long – and not guaranteed – way of improving public health and accessing health innovation.

One of the most important issues is defining health priorities. This definition can change the evaluation of the balance between cost and effect in an artificial way. For instance, if a country goes through an epidemic, it will more likely adopt measures, reimburse medications, and undertake tests, with the objective of stopping and controlling a particular public health emergency. Ideally, if cardiovascular diseases are an important cause of death in a specific country, measures to control hypertension or dyslipidemia are more likely to be adopted. Cancer is already the leading cause of death in several developed countries, and it is expected to be the leading cause of death in Brazil in the near future.

Solutions from other countries: controlling drug costs

The obvious balance between cost and effectiveness, which would change this equation in the sense of improving access to innovation, and, ultimately, improving public health, would be: (i) decreasing the cost; or (ii) increasing the effectiveness of a given medical technology.

Measures to control drug prices have been adopted in many countries. Italy has implemented a health policy founded on performance-based agreements. This is a model of sharing responsibility and risk between the public health system and the pharmaceutical companies. It happens in three ways: (i) cost sharing, consisting of a discount on the initial price of treatment for all patients; (ii) risk sharing, when price discounts are applicable to the initial therapy cycles of non-responder patients; and (iii) payment by results, when the initial cycles are fully reimbursed by the pharmaceutical company if no effect is observed (37).

Most governments control the initial prices of reimbursed medicines. They are often the biggest buyer, which allows for negotiating prices, establishing reference prices, and establishing reimbursement levels and restrictions. In Europe, some countries allow companies to freely determine the initial drug launch prices. However, price controls may apply by using paybacks and volume agreements. Another practice to control costs is sharing it with the patients; co-payments make patients cost-sensitive and add another layer of control at the consumer end.

Drug research and improvement in drug access

In the context of reducing drug costs, biosimilar drugs can play a major role, as biological agents account for 42% of the drug expenditure in Brazil (38). Biosimilars differ from generic drugs because they are biologically complex molecules that are synthesized by living cells, whereas generic drugs are manufactured by simple chemical reactions. According to the USA's Federal Drug Administration (FDA), a biosimilar drug "has no clinically meaningful differences in terms of safety and effectiveness from the reference product" (39). Being less expensive than the originator product, biosimilars have the potential to reduce the costs related to cancer treatment and to improve drug access in countries where their cost makes it prohibitive. In general, they can decrease the drug cost by approximately 30%-40%, and in some cases prices could be even 70% below the cost of the originator drug (40).

Despite using the term "biological drug" and not "biosimilar," the regulations to approve such drugs in Brazil are similar to that of the FDA (41, 42). As a new initiative, the Brazilian government has stipulated that pharma companies must develop products that are classed as public health priorities, and it has stated those public health priorities, including the drugs and equipment required. In 2015, the list of biological drugs included adalimumab, filgrastim, infliximab, rituximab, and somatropina. Agreements with companies that support this initiative are beneficial for both sides: the pharmaceutical companies and the Brazilian government. The agreements include guarantees for the companies selling large amounts of their products in exchange for the transfer of technology to the Brazilian labs. This will foster the Brazilian research and development of drugs tailored to the public health problems of its population. In 2016, the first monoclonal antibody was approved in Brazil: infliximab (Remsima™) for the treatment of rheumatologic diseases (43). However, to date, there are no biosimilar oncologic active drugs approved by ANVISA. Earlier, in 2015, a trastuzumab biosimilar, manufactured by the Korean company Celltrion was rejected; however, in the same year, a biosimilar filgrastin was approved, being the first biosimilar drug to be totally produced in Brazil (44).

Today there are 16 private pharma companies and 6 public labs working together for the development of 14 biosimilar drugs for multiple indications ranging from cancer to diabetes and inflammatory diseases, and for the production of vaccines. In the oncologic field, the partnership hopes to produce biosimilar versions of bevacizumab, cetuximab, and trastuzumab in local laboratories (38).

Developing more effective drugs

Clinical research can affect the cost-effectiveness balance, not only by creating less expensive versions of approved drugs, but also by developing more effective innovative compounds.

With more effective drugs, the monetary value invested would result in better clinical outcomes per money spent.

There are initiatives from several oncologic societies, such as the American Society of Clinical Oncology (45) and the European Society for Medical Oncology to evaluate not only the statistical significance of a study result, but also the clinical relevance of the relevant drug in daily clinical practice (46). In the future, new clinical trials would, ideally, be designed to detect results not only with statistical significance but also with clinically significant magnitude.

This is a complex task as it involves a deeper understanding of the disease mechanism and the identification of predictive biomarkers of response. When biomarkers are not available, it does not mean that the drug cannot be effective; however, from a public health point of view, the results can be less impressive (47). Initiatives to develop tools to evaluate the magnitude of clinical benefit can help to frame an appropriate use of limited public resources (46).

Conclusion

An effective health system must be able to deal with the problems of its population. In a context of limited resources, the decision for budget allocation on a specific health intervention must be in line with the health priorities of each population. Decisions for incorporation must be evaluated taking into consideration the drug's possible improvement of the public health in relation to its monetary impact on the health budget.

Measures to improve access to newer compounds, while maintaining affordability, can be taken in many steps of the process. The definition of budget allocation and health priorities is a societal decision that must be democratically discussed.

Health authorities have a primary role because they can implement strategies to control drug prices. Already in place in many countries, the strategies of risk sharing, negotiating volume sales, rebates, and/or profit limiting can decrease the price of drugs and allow the allocation of resources to new compounds, or increase the acquisition of drugs with greater demand.

From the research perspective, the development of biosimilars (as with generic drugs) can substantially decrease the cost of drugs that are no longer under patent protection, thereby saving resources for acquiring innovative drugs. Local production of such agents also has the potential to decrease costs.

Brazil, like other developing countries, should develop strategies to foster local research aimed at the specific health problems of its population. Tailored research, with the local production of biosimilars and innovative drugs, has the potential to develop more effective medicines adapted to local problems and to reduce production costs. Ultimately, all these strategies would improve the effectiveness of a health system while maintaining its affordability.

Key messages

Brazil is a developing country with huge inequalities, which also include access to health care.

The Brazilian population is ageing and an increase in cancer incidence is expected in the near future.

Proactive measures to deal with the future extra cancer burden have to be implemented as soon as possible. Measures to maintain an effective and affordable health system should include:

- Defining health priorities and allocating resources to health care.
- Controlling the cost of drugs and other health technologies.
- Investing in research tailored to the health problems of the population and the production of less expensive alternatives of treatment, such as biosimilar drugs.

Disclosures

Financial support: No grants or funding have been received for this study.
Conflict of interest: No potential conflict of interest was reported by the author.

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