CRA Charles River Associates

ASSESSING THE VALUE OF BIOPHARMACEUTICAL INNOVATION IN KEY THERAPY AREAS IN MIDDLE-INCOME COUNTRIES

TIM WILSDON
JIM ATTRIDGE
EVA FIZ
SATOMI GINOZA
ADAM MITCHELL-HEGGS

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EXECUTIVE SUMMARY

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the value of innovation in middle-income countries (MICs) and to test the extent to which the experience of these countries is aligned with the experience of high-income countries (HICs). The project has three goals, to:

- Investigate the value of biopharmaceutical innovation, by observing how treatments have evolved for a set of therapy areas;
- Highlight the benefits and cost savings using data from MICs and HICs;
- Consider the lessons and policy implications.

CHOICE OF CASE STUDIES

In order to achieve a balanced perspective, the report covers a number of therapy areas where there is a high disease burden in MICs, and representing both communicable and non-communicable diseases (NCDs). In addition, it includes therapy areas where there are mature classes of medicines and where innovation is more recent. The evolution of classes of innovative medicines is a highly unpredictable process driven by a combination of scientific push forces, unmet need and economic opportunity representing market pull forces. Even in HICs the diffusion of innovations into general clinical practice usually only occurs slowly over many years and can vary significantly from country to country – with the result that value can often only be observed after some period of time. Historically, this delay in access has been much greater in MICs, where there are far more significant technical and economic barriers to uptake. In consequence, it is important to consider therapy areas where the innovative medicines for treating them have emerged over different time frames. We therefore chose to focus on five disease areas: coronary heart disease (CHD), depression, diabetes type II, HIV/AIDs, and rotavirus infections.

In terms of choosing the countries to be included in the analysis we have used two approaches:

- Comparing across different MICs – this was the approached used for CHD, depression and HIV;
- Compared the value in a MIC directly to that observed in a HIC – this was the approach used for rotavirus and diabetes type II.

Table 1: Country selection by therapy area

THERAPY AREA	COUNTRIES INCLUDED IN ASSESSMENT
CHD	Brazil, China, India, Russia and South Africa
Depression	Brazil, China, India, Russia and Chile
Diabetes	HIC (represented by Australia, Canada and UK), MIC (represented by China)
HIV/AIDS	Botswana, Brazil, China, India and South Africa
Rotavirus	HIC (represented by Australia), MIC (represented by Brazil)

Source: CRA analysis

This pragmatic approach to identifying the most relevant evidence means although we focus on the added value in the BRICs for most case studies, we have included a number of other MICs that have particular relevance to the study.

ASSESSMENT OF VALUE

We have classified value, which accrues to MICs through the uptake of modern medicines, as falling into three general categories; the clinical benefit to patients, the impact upon health system costs and wider societal benefits.

From a methodological perspective the evidence base also consists of studies of different types: academic international comparisons, reports by organisations such as the WHO, reports derived from clinical research, analysis undertaken as part of the clinical or economic assessment of these medicines.

CHD

There was a golden age of innovation in new classes of effective treatments for serious cardiovascular diseases over the years 1970-1995. Notably advances for treating angina, hypertension, hypercholesteraemia and heart failure. In each case a range of closely related innovative active agents have been developed, providing clinicians with a choice to select a treatment to suit the needs of individual patients. More recently there has been a steady series of incremental advances in the form of new molecules, slow release formulations and fixed dose combination products to support improved adherence to, and effectiveness of, these chronic therapies. As today virtually all of the members of these classes have patent expired they are available globally as generic products at very low prices. Indeed, in many cases they are manufactured within MICs, notably in India and China.

For MICs, CHD is a major issue in terms of mortality and the years of life lost due to premature death and disability. WHO statistics show that within MICs more than 5 million people died as a result of the disease in 2008. Despite this massive burden of disease it is only in recent years, within the context of broader initiatives to tackle NCDs, that national strategies to reduce the burden of CHD have been proposed and to some limited degree implemented. Looking at selected MICs, only Brazil, India and China have a national plan, and even these were started only within the last three years. Therefore, it is still relatively early to assess their impacts. In many cases, most notably in India, these plans have been subject to delays or cutbacks in practice, due to lack of funds and bureaucratic inefficiencies.

In terms of access, all the selected countries have included at least one molecule in each class in their essential drug list (EDL), which in principle means that the molecules should be widely available to the population. However, this depends on adequate primary care capabilities to diagnose, treat and monitor patients. Only Russia and South Africa have specific guidelines for the treatment of CHD. Looking at the existing evidence within the selected countries, we found that use of cardiovascular drugs varies substantially from country to country. Molecules that have been in the market for many years and are very inexpensive, such as aspirin, are widely used in most countries, whereas statins, which are relatively more expensive and require

laboratory testing facilities to test cholesterol levels before an appropriate drug and dosage level is selected, are less commonly used, despite the strong evidence for their effectiveness and increasingly high levels of uptake in developed countries.

The evidence that the treatment for CHD has brought clinical and therapeutic benefits within the BRICS is mixed. With the exception of China, CHD-caused mortality rates decreased between 2002 and 2008 in all the selected countries, however, given the lack of any correlation between access and reduced mortality, it is difficult to attribute this directly to access to medicines. On the other hand, clinical research has shown the efficacy of these products in these markets. There is also country-specific evidence from the case study countries and international evidence that an improvement in access to CHD treatment has led to a further reduction in the burden of CHD. However, we conclude that only limited evidence exists showing the link between the use of cardiovascular drugs and other benefits, such as cost savings or wider socio-economic gains such as labour productivity and lower social care costs.

Overall, there is evidence of value but there appears a significant opportunity for further health gains from the more widespread deployment of these innovative medicines from past decades. Table 2 summarises the main findings of the CHD study.

Table 2: Summary of the findings related to treatment, usage and value of medicines for CHD within BRICS

	BRAZIL	RUSSIA	INDIA	CHINA	SOUTH AFRICA
National strategy against CVD	NCD plan 2011-2022	N/A some efforts started	NCD plan 2010	NCD plan 2012-2015	N/A
Inclusion in EDL	Yes	Yes	Yes except statins	Yes	Yes
Use of CVD drugs*	48%	65%	55%	58%	No reliable estimate
Existence of treatment guidelines	No	Yes	To be implemented	No	Yes
Evidence on the value of treatment	Clinical	Clinical	Clinical	Clinical	Clinical

Source: CRA analysis; *Calculated using the average use of the selected drugs in Figure 12

DEPRESSION

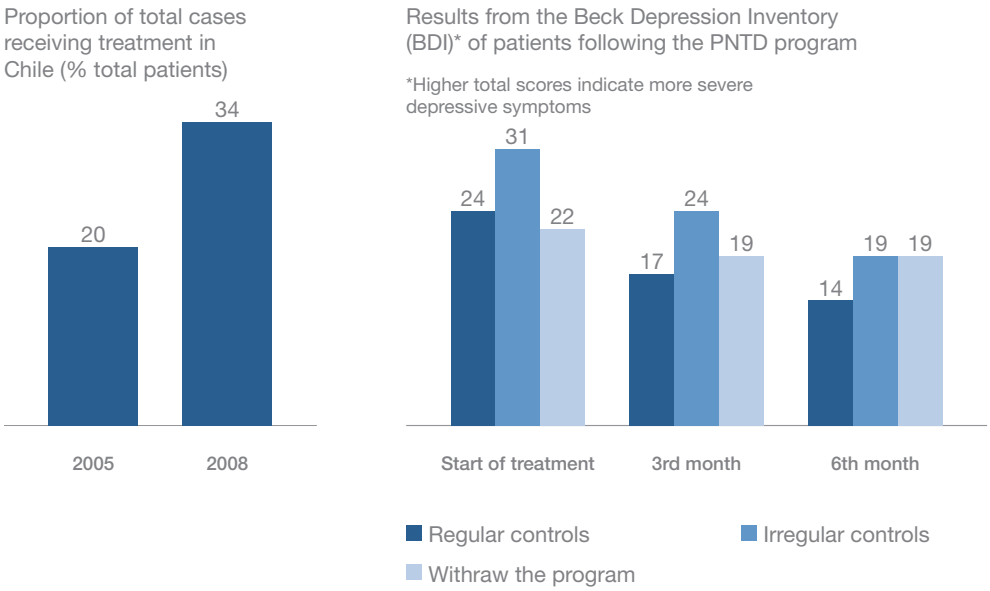
Depression is a common mental disorder that has significant consequences for the patient's quality of life and at its worst, depression can lead to suicide. It has a high burden of disease within the MICs in terms of health years lost. Although mortality due to depression is relatively low, accounting for less than 0.05% of deaths due to NCDs, the number of DALYs lost was as high as 48.5 billion DALYs across the MICs, accounting for 9% of DALYs lost due to NCDs.

There are several classes of antidepressants with different mechanism of actions. All antidepressants are similarly effective in treating moderate to severe depression, but they differ in terms of adverse effects.[1] Selective serotonin reuptake inhibitors (SSRIs) were launched in the mid to late 1980s, although some were launched in the last few years. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a newer class of antidepressants that developed after 1990, and there are fewer molecules in this class.

Regarding access, very few MICs have national strategies targeted specifically at depression. Most of the MICs studied – Brazil, Russia, India, and China – only have national mental health policies, which are geared more towards psychotic conditions than depression. Only a few countries, as illustrated by Chile have a program specifically aimed at depression. In the case of Chile, this was expanded nationally in 2003. Even so, all the selected countries have at least a molecule from two antidepressant classes on their EDL, meaning that in theory they should be widely available to the population and given their maturity will have generic competitors. Additionally all of the selected countries except for Russia have guidelines regarding the use of antidepressants among depression sufferers. However, despite the availability of medicines, evidence suggests that depression is rarely treated in MICs. There are estimates that of the selected countries, only around 10% of people with depression see a healthcare professional or receive medication for the condition. The exception is Chile, where 20% of depression sufferers received treatment and, after the inclusion of depression as a priority health issue, the percentage treated increased to 34%.

In terms of value, there is evidence that the treatment for depression delivers clinical and therapeutic benefits within the selected countries. The evidence from the Chilean programme is set out below.

Figure 1: Improved clinical outcomes in Chile



Source: Bitran et al (2010), "After Chile's health reform: increase in coverage and access, decline in hospitalization and death rates", Health Affairs 29(12): 2161-2170; Alvarado and Rojas (2011), "El programa nacional para el diagnóstico y tratamiento de depresión en atención primaria: una evaluación necesaria", Revista Médica de Chile, 139.

1 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

There clearly remains a significant issue associated to awareness but this suggests that given a targeted plan and the health system is given sufficient resources to diagnose and manage patients, medicines for depression can deliver considerable value.

There is more limited evidence regarding the link between the use of antidepressants and non-clinical benefits. Very few papers examined the effect on cost savings and socio-economic elements. However, there were papers that found less functional impairment and fewer lost workdays among people with less severe depression. This suggests that if a greater number of depression sufferers in MICs receive treatment, the clinical benefits could translate into wider gains for society. There is evidence in HICs that antidepressants result in lower productivity losses, suggesting that if depression were more frequently diagnosed and treated in MICs, antidepressants could bring greater value, a hypothesis that is supported by a WHO DALYs saved projection study. Table 3 summarises the main findings of the depression study.

Table 3: Summary of the findings related to treatment, usage and value of medicines for depression within BRIC + Chile

	BRAZIL	RUSSIA	INDIA	CHINA	CHILE
National strategy against depression	Mental health policy, 1991	Mental health strategies	National Mental Health Programme (NMHP), 1982	Mental health plans	National Depression Program (PNDTD) 2003
Inclusion in EDL	TCA, MAOI, SSRI, other	TCA, SSRI	TCA, SSRI	TCA, MAOI, SSRI, SNRI, other	TCA, SSRI, SNRI, other
Treatment received*	17%	3%	8%	9%	27%
Existence of treatment guidelines	Yes	No	Yes	Yes	Yes
Evidence on the value of treatment	Clinical	Clinical	Clinical	Clinical	Clinical; Cost control

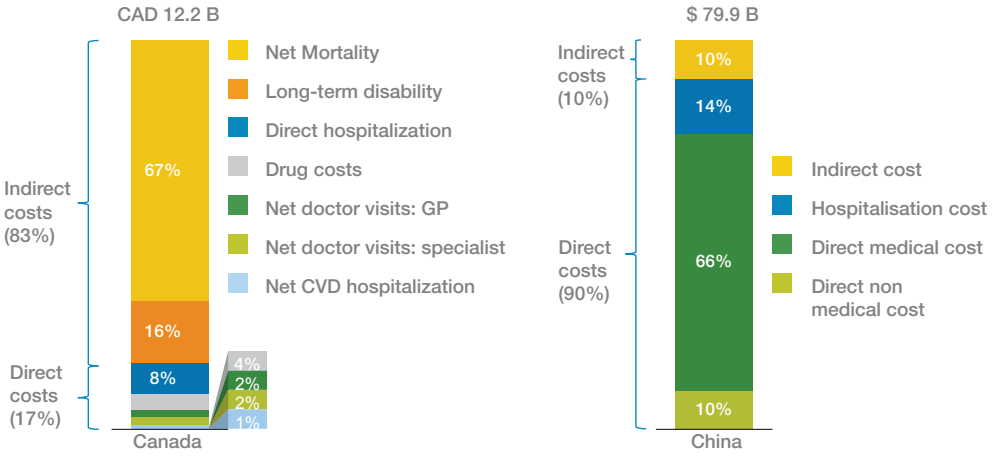
Source: CRA analysis; *Treatment rates for any kind of treatment received for depression, pharmacological and non-pharmacological; Analysis using country-specific sources [2]

DIABETES TYPE II

The improved economic status and the adoption of western life styles across society in MICs, notably poor diets and lack of exercise, is driving the incidence and prevalence of diabetes, often undiagnosed and untreated, to unprecedentedly high levels. This is creating a massive health challenge. Diabetes is a lifelong disease that requires a complex and delicate management of glycaemic control and prevention of acute long-term complications to manage the significant economic burden that would otherwise fall on HICs and MICs.

2 Brazil and Russia: Simon et al (2004), 'Prevalence and predictors of depression treatment in an international primary care study', Am J Psychiatry 161:9; India: average of low and middle income countries, Academy of Medical Sciences (2008), 'Challenges and priorities for global mental health research in low- and middle-income countries'; China: Zhang (2010), 'Major depressive disorder treatment guidelines in China', J Clin Psychiatry 71: e06; Chile: Bitran et al (2010), 'After Chile's health reform: increase in coverage and access, decline in hospitalization and death rates', Health Affairs 29(12).

Figure 2: Burden of Diabetes in HICs and MICs



Source: CRA analysis using Canadian Diabetes Association (2009), 'An economic tsunami the cost of diabetes in Canada'. Note: CAD – Canadian dollars and Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', The American Journal of Managed Care, 15,9

It is one of the most common NCDs in the world, with similar prevalence rates in HICs and MICs as of 2012. However, the number of individuals suffering from diabetes is significantly larger in MICs (around 374 million) compared to HICs (75 million) simply due to relative size of population.

There has been considerable advance in the medicines available for treating diabetes. Diabetes is normally treated by using insulin therapy as a replacement therapy and/or by controlling blood glucose levels with oral anti-diabetic drugs (OAD). The IDF recommends metformin as a first-line treatment, and other glucose control agents such as sulphonylurea as a second-line treatment. Newer OADs such as AGI, meglitinides and thiazolidinediones were introduced in the early 1990s, and further innovative agents such as GLP-1 agonists and DPP-4 inhibitors were launched in the mid-2000s.

Diagnosis, treatment and management of diabetes are very well defined in HICs. The access to treatment in MICs appears significantly less complete. Diabetes care in China has limited infrastructure, and the delivery of healthcare varies considerably by location. Additionally, there is a lack of diabetes awareness in China, resulting in relatively low rates of diagnosis – about 10%-15% of people with T2D are diagnosed, compared to a 50% diagnosis rate in Europe.[3] Furthermore, access to monitoring is also limited. The Diabcare-China study of T2D participants showed the following:[4,5]

- More than half of the people with diabetes had poor blood glucose control (glycaemic control).
- Half of the people had their HbA1C (an indicator of long-term blood glucose levels) measured in the last 12 months.

3 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

4 The Diabcare-China study collected data from a cohort of 2,700 people with diabetes at 30 specialist centres across China.

5 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

- About three in five people with diabetes had poor metabolic control, showing above-average levels of triglycerides and LDL cholesterol (so-called 'bad' cholesterol).

However, insulin and oral hypoglycaemic drugs are included on the Chinese EDL, meaning that some treatments are available. Additionally, the Chinese government has recently launched the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, which aims to develop a plan for NCD including diabetes.

Studies have shown that appropriate treatment, close monitoring and behavioural changes can delay or prevent the progression.[6] We found evidence that diabetes therapies have brought value in HICs in terms of clinical benefits and reduction of healthcare costs, as well as wider socio-economic benefits such as the avoidance of DALYs lost. Diabetes treatments have also yielded clinical benefits in China when they were used, and there is evidence that effective treatment results in savings to the health system. Treatment has also been shown to reduce lost productivity among diabetics in China, although since indirect costs were a smaller portion of the societal cost of diabetes in China compared to HICs, the savings per person is not as large. Table 4 summarises these results.

Table 4: The value of treatment for diabetes: HIC vs. China

	HICS	CHINA
Therapeutic/clinical value	✓	✓
Controlling costs	✓	✓
Wider benefits	✓	Limited

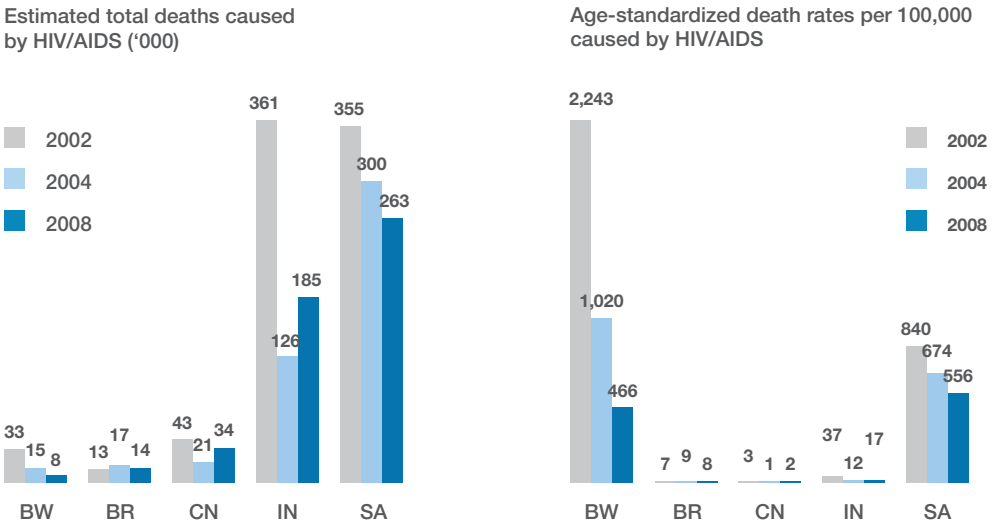
Source: CRA analysis

HIV/AIDS

HIV/AIDS is a severe disease, and addressing it became a national priority, especially for many MICs (and LICs). Significant steps have been made to address this challenge over the last two decades. The number of people living with the disease is stabilising, and the mortality and DALYs level has decreased significantly both in MICs and in the selected MICs. Furthermore, the level of transmission between mother and unborn child has decreased significantly.

6 Wang (2011), 'Diabetes care in China. Impacts of Traditional Chinese Medicine (TCM) and insurance on quality and utilization', dissertation for doctoral degree at the Pardee RAND Graduate School.

Figure 3: Burden of HIV/AIDS within selected MIC



Source: CRA analysis using WHO Statistical Information System (WHOSIS), Global burden of disease. Available here http://www.who.int/healthinfo/global_burden_disease/gbd/en/index.html Last accessed: July 2013. Note: Botswana (BW) Brazil (BR), India (IN), China (CN), South Africa (SA)

It is evident that access to ART, in combination with improvements in prevention and diagnosis, has played a significant role. Access to improved FDCs is likely to have had a positive impact in markets where they are available, due to increased adherence. This represents both radical and incremental innovation – through a series of increasingly effective active materials (radical) and responding to the need for incremental advances in delivery mechanisms and product formulations to reduce the complexity of daily dosage regimes to achieve continuity of adherence to treatment protocols in large unsophisticated patient populations.

In addition to clinical and therapeutic benefits, there is also evidence that the introduction of these policies and access to ART is beneficial economically, through reduction in other healthcare costs (such as hospitalisations), and socio-economically, through reduction of absenteeism and improvements in HIV/AIDS patient quality of life. Table 16 provides a summary of the findings within the selected countries.

Table 5: Summary of the findings related to treatment, usage and value of medicines for HIV/AIDS within selected MICs

	BOTSWANA	BRAZIL	CHINA	INDIA	SOUTH AFRICA
National strategy against HIV/AIDS	2001	1986	2003	During 1980s	2004
Inclusion in EDL	Yes except integrase, and fusions and entry inhibitors	Yes except fusions and entry inhibitors	Yes through Free ART	Yes except integrase, and fusions and entry inhibitors	Yes except integrase, and fusions and entry inhibitors
Use of ARTs	83%	70%	29%	26%	37%
Evidence on the value of treatment	Clinical, Socio-economic	Clinical, Cost control; Quality of life	Clinical	Clinical; Socio-economic	Clinical, Cost control; Socio-economic; Quality of life

Source: CRA analysis

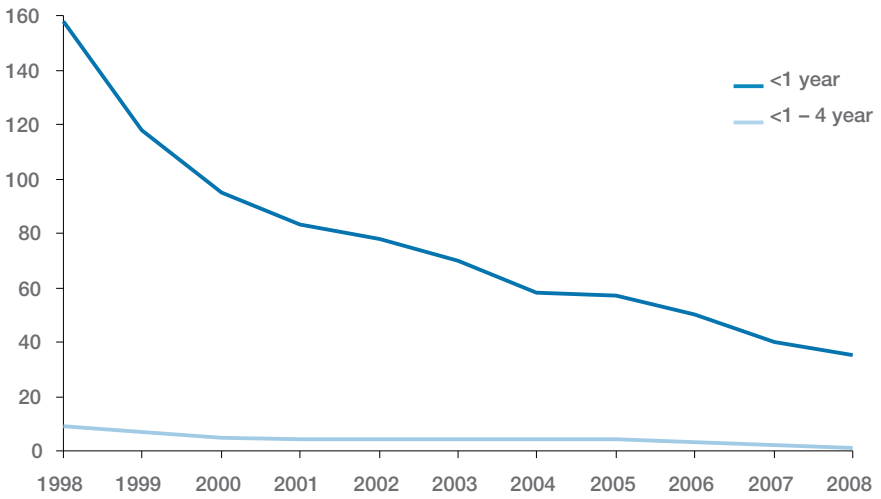
ROTAVIRUS

Diarrhoea is a leading killer of young children worldwide, and rotavirus is the most common cause of severe diarrhoea. Rotavirus diarrhoea is a significant cause of clinic visits or hospitalisation among children in both industrialised and developing countries.

Two vaccines against rotavirus were launched in 2006 and 2008. A number of countries have included a rotavirus vaccine in their National Immunisation Program but our analysis focused on the experience in a HIC (Australia) and a MIC (Brazil) that nationally provided rotavirus vaccination around 2007. Two years after the introduction almost 80% of their young children were covered by the vaccine.

Rotavirus vaccination programs have been shown to bring a wide range of benefits within both HIC and MICs. In Australia, the biggest benefit we observed was related to the reduction in hospitalisation costs, while in Brazil we observed clinical and therapeutic benefits as well as those related to hospitalisation costs. In particular, the rotavirus vaccine has led to a dramatic reduction in gastroenteritis-related deaths in Brazil.

Figure 4: Gastroenteritis-related deaths by age group, Brazil, 1998-2008



Source: Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International Journal of Infectious Diseases, 15

These results reflect the fact that rotavirus-related mortality is almost non-existent within HICs while is still significant within MICs.

Table 6: The value of rotavirus vaccines: Australia vs. Brazil

	AUSTRALIA	BRAZIL
Therapeutic/clinical value	✓	✓ (including a significant impact on mortality)
Controlling costs	✓	✓
Wider benefits	✓	✓

Source: CRA analysis

Rotavirus therefore provides a case study where both HICs and MICs clearly benefit from the introduction of an innovative medicine but where MICs are likely to receive a wider variety of benefits than HICs.

POLICY IMPLICATIONS

Finally, we were asked to use the case studies to draw lessons and the policy implications regarding the relationship between achieving medical progress and societal health gain, by extending access to innovative medicines. Learning from the case studies, we draw five policy conclusions:

1. **Ensuring that the widest population receives the value of innovative medicines often requires a national programme to increase awareness and overcome cultural challenges**

If we consider the therapy areas where there is the clearest evidence of value being delivered in MICs, this typically occurs once this has been recognised as a priority area at the national level. HIV/AIDS and, to a less extent, rotavirus have been a major focus of governments in the case study countries. This has clearly meant that resources were assigned to ensure access to treatment. In both of these areas, clinical benefits, healthcare savings and societal benefits have been achieved since the introduction of innovative treatments.

For NCDs, political prioritisation also appears important, particularly, where the main limitations that are preventing the benefits of innovative treatments from being brought to MICs are the healthcare infrastructure and cultural barriers. Only in recent years, have we seen CHD, depression, diabetes being given significant attention and therefore it is not surprising that the evidence on benefits today are limited. This appears especially important where cultural obstacles are the main barrier, for example, with mental illnesses such as depression. However, as illustrated by Chile, where these become a policy priority, significant progress can be made.

However, it is also clear that in some MICs there have been "false dawns" where national programmes have been announced but where ultimately they have not resulted in patients receiving the value of innovative medicines. Establishing the therapy area as a policy priority is clearly only a necessary but not sufficient condition for this to occur.

2. **For medicines to deliver value, there needs to be appropriate healthcare infrastructure, this works best when integrated programmes are used to ensure diagnosis, testing, access to medicines and maintenance of patients on a course of treatment**

For CHD, diabetes or depression, for example, the main barrier to treatment is that patients suffering or at risk of suffering from these diseases are not always diagnosed. It is self-evident that the necessary health system, clinical infrastructures for diagnosis, treatment and follow-up needed to extend access or distribution systems do not always exist. The availability of specialist doctors per patient population is significantly smaller in MICs than in HICs.

In addition, some diagnosis protocols require advanced equipment that is only available in larger cities and for a particular set of patients. Therefore, even if the treatment are relatively inexpensive, as are drugs for CHDs or depression, patients are not able to get access, as their illness has not been diagnosed.

The largest benefits have been achieved in those therapy areas where the infrastructure required to introduce innovation is smaller or where it has been seen as a priority (and hence significant investment in infrastructure undertaken). Rotavirus vaccination is an example of a therapy area which requires relatively little investment in infrastructure. Given sufficient resources, high levels of access can be achieved such as in our case study country Brazil.

In contrast, CHD, diabetes and depression are therapy areas that require the availability of specialists or sophisticated technology. Indeed, as not all the population has access to specialists who are able to define and monitor the treatment, the achievement of benefits within these therapy areas is limited. This is particularly relevant to depression, which requires a combination of pharmacological and psychological treatment.

This requires adequate healthcare resources and government capital and revenue funding being consistently allocated to building these infrastructures over time. Capturing the value of innovative medicines, especially for NCDs, requires an integrated policy developing the infrastructure to diagnose and manage patients, as well as access to innovative medicines.

3. The healthcare system needs to incorporate both incremental and radical innovation

The benefits from innovative treatments have been delivered through different types of innovation. We find that whether the innovation is perceived as radical or incremental is not associated with the value achieved.

Most would characterise rotavirus and HIV/AIDS as involving radical innovation. However, it is clear that the development of classes of medicines for HIV, fixed dose combinations and targeting the medicines on new patients groups has brought significant value to patients and society more generally.

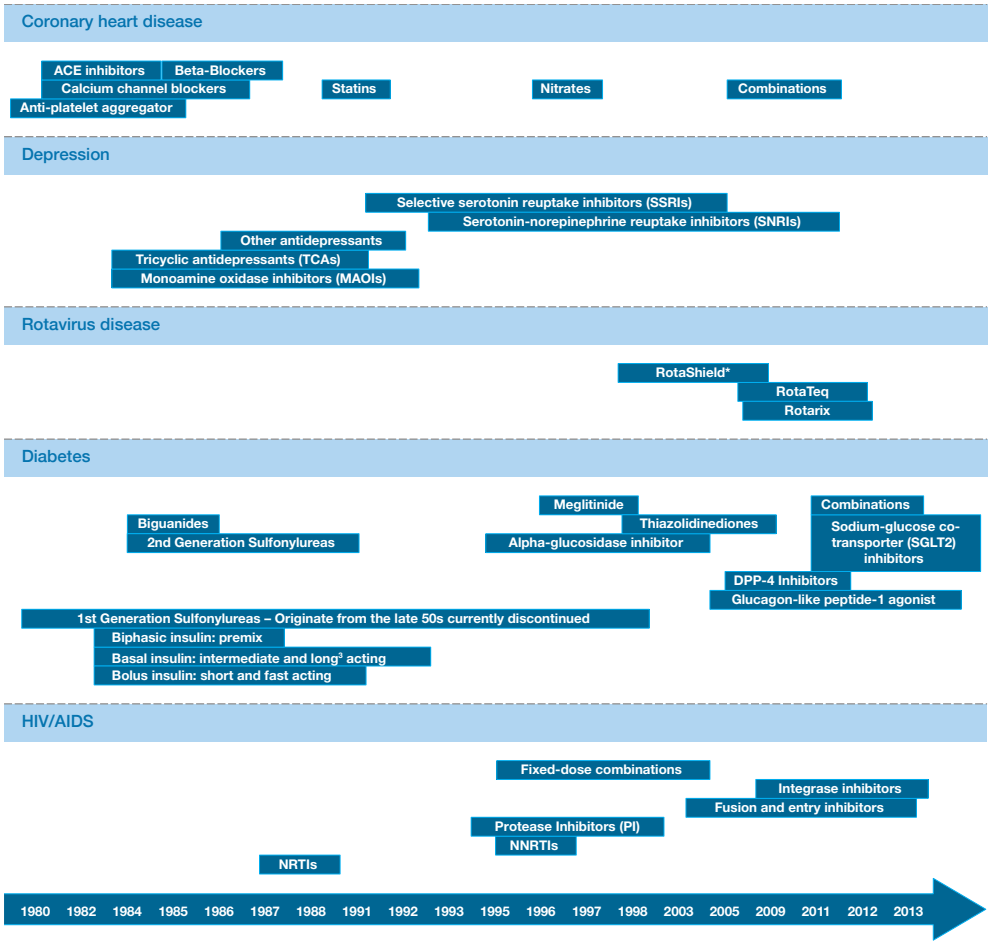
Another example can be found by looking at CHD and depression, where new treatments have been developed both by creating new classes of medicines and by creating new molecules within a class. This has reduced side-effects and improved tolerability for depression and new classes of medicines for CHD have benefited different patient groups. Although the benefits achieved within MICs are still far from what could be reached, CHD is a good example of a therapy area where benefits can be delivered through both radical and incremental innovation.

4. There is not a simple relationship between whether we can observe value and the current intellectual property protection of the medicines

Based on the case studies chosen for this project, we found that the current status of patent protection does not inhibit the value of the innovation to society. The study

shows value to society being delivered by both patented and off-patent medicines. Indeed, in the therapy areas where treatments have brought the greatest value, rotavirus and HIV/AIDS, the medicines used are still protected. In contrast, in therapy areas where the existing treatment has been on the market since the '80s and is now off-patent, and low-cost drugs are available – depression and CHD – only limited benefits have been realised and there is still significant value to be extracted. Figure 5 illustrates the maturity of the different therapy areas we have examined.

Figure 5: Development of innovative treatment in the selected therapy area and class



Source: CRA analysis

Whether we can observe the value of different classes is not directly related its intellectual property protection and both patented and off-patent products can deliver value to MICs and HICs.

5. In MICs, as in HICs, value can be delivered directly to patients, in terms of cost savings to the healthcare system and to wider society, this needs to be reflected in how medicines are assessed

Innovative medicines have delivered a broad range of benefits affecting not only patients but also the healthcare system and the society in general. We tested this directly by comparing the composition of benefits delivered in a MIC versus a HIC. Evidence shows that the full range of benefits can be achieved in both HICs and MICs and for some therapy areas a wider variety of benefits is achieved in MICs than HICs. The rotavirus

vaccination provides a good example of a therapy area for which innovation has brought value to patients but also wider benefits. After the introduction of the rotavirus vaccine into the immunisation programs of both Australia and Brazil, not only was there a reduction of child mortality rates due to gastrointestinal diseases (primarily affecting Brazil) but also a reduction of healthcare-related costs was achieved as the hospitalisation rates related to gastrointestinal diseases were significantly reduced in both Australia and Brazil.

Looking at the other case studies, we also found evidence of value being delivered through reduced healthcare costs (CHD, diabetes) and through benefits to the wider economy (HIV).

There is considerable scope over the long term for MIC health authorities to refine their approaches to assessing the value of modern medicines from a national perspective. We would recommend therefore that a modest investment of central resources in building better epidemiological and cost databases to support the development of modern methods of evaluating the relative value of alternative therapies.

CONCLUSION

The purpose of this paper was to set out the evidence that innovative medicines deliver value in MICs and to compare this to evidence from HICs. In all of the therapy areas considered these is evidence of value delivered but it is clear that the quality of the evidence is weaker than in HICs. It is also the case, that the existing evidence for communicable diseases is stronger than for non-communicable diseases.

In terms of types of value, we find innovative medicines deliver value to patients but also through a reduction in healthcare costs and to wider society in MICs and HICs – the categories are often the same, even if, the composition of this does vary in MICs compared to HICs. In some cases, medicines offer greater benefits in MICs and in some cases less.

The extent of access to medicines is a significant factor in the value they deliver. The cost of medicines has an impact on how widely they are used, but we have found that the value delivered within innovative treatment across MICs depends on several other elements: whether governments have chosen to prioritise that particular therapy area and the availability of the appropriate infrastructure to implement the innovation.

It is also clear that value of medicines occurs through both radical innovation, offering a treatment where none previously existed but also through incremental innovation, reducing side effects, expanding choice of treatments or widening the patient population. This brings value to MICs, just as it does in HICs.

In summary, the case studies illustrate well the remarkable range and diversity of biopharmaceutical innovations which have added value across all MICs to some degree. It also reinforces the message that there remains enormous untapped potential to improve patient outcomes by adopting them more widely. In some cases fewer than 10-20% of the relevant population currently have access to these important advances in therapy. Whether we can observe value being delivered to MICs varies between the

therapeutic areas considered and can only be explained by considering a range of different factors. A summary of our findings is presented in Table 7.

Table 7: Summary table

	EVIDENCE ON OVERALL BENEFITS ACHIEVED IN MICS	EFFECTIVE CLASSES OF TREATMENT	GOVERNMENT PRIORITY	INFRASTRUCTURE REQUIRED	TYPE OF INNOVATION
CHD	Medium	Significant impact across range of conditions	Recent	Medium	Radical & Incremental
Depression	Limited	Effective for some patients but still significant unmet need	No	Large	Radical
Rotavirus	Compelling	Significant reduction in risk of mortality	Yes	Minimum	Radical
Diabetes	Medium	Transformed into a chronic conditions and avoided significant health issues	No	Medium	Incremental
HIV/AIDS	Compelling	Transformed to a chronic condition for many	Yes	Medium	Mixed

Source: CRA analysis

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INTRODUCTION

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the value of innovation in middle-income countries (MICs) and to test how the experience of these countries compares to that of high-income countries (HICs). The project has three goals, to:

- Investigate the value of biopharmaceutical innovation, by observing how treatments have evolved for a set of therapy areas;
- Highlight the benefits and cost savings using data from MICs and HICs;
- Consider the lessons and policy implications.

1.1. BACKGROUND

Over the last ten years, the industry and academia have put together a range of evidence on the value that medicines bring to society. There have been papers setting out the different components of innovation,[7] studies attempting to quantify aggregate benefits that new medicines bring[8] and studies looking at the range of case studies illustrating the value that medicines deliver during the patented period.[9] In each of these areas, there is now a body of evidence in the US and increasingly in European markets regarding the value of innovation in terms of case studies and empirical evidence. However, there is relatively little evidence on the value of innovation to emerging markets.[10] This report is intended to complement and build upon the existing IFPMA commissioned research publications on innovation and access.[11]

The overall objective of this project is therefore to determine whether there is evidence that innovative medicines deliver value to MICs, and the extent to which this reflects radical innovation or incremental innovation.

1.2. DEFINITION OF INNOVATION AND VALUE

There are different types of innovation. Innovation is often classified as either revolutionary, radical or incremental. Figure 6 illustrates the different types of biopharmaceutical innovation. The term 'revolutionary innovation' can be applied to major conceptual advances, such as the identification of microbes and classes of anti-infection agents. A new understanding of a disease mechanism and a new mode of action that

7 'The Many Faces of Innovation' by OHE Consulting for the European Federation of Pharmaceutical Industries and Associations (EFPIA), 18 February 2005.

8 Lichtenberg, 2010, 'The Contribution of Pharmaceutical Innovation to Longevity Growth in Germany and France' CESifo Working Paper Series No. 3095 or Lichtenberg, 2003. 'The Impact of New Drug Launches of Longevity: Evidence from Longitudinal, Disease-level Data from 52 Countries, 1982-2001', NBER Working Paper Series.

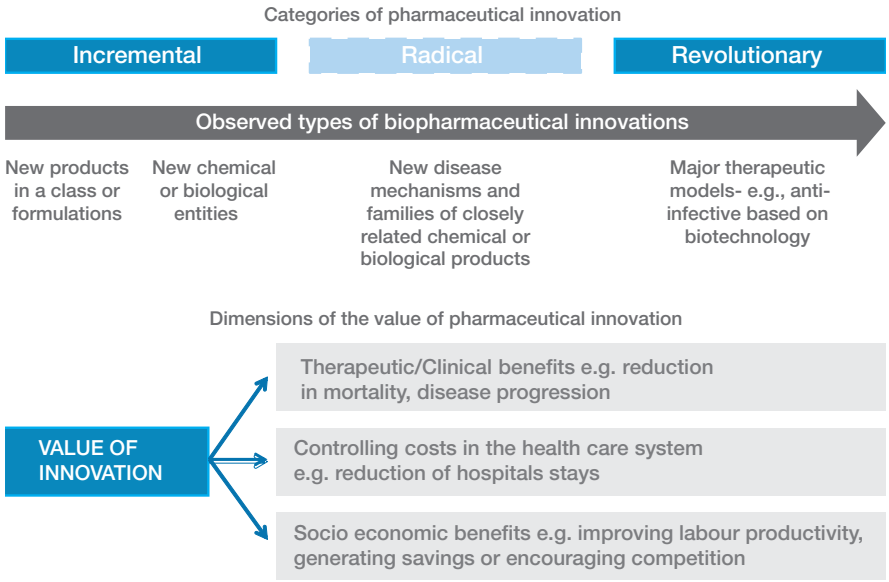
9 PhRMA 'Pharmaceutical Industry profile'.

10 The exceptions to this are the IFPMA report 'Incremental Innovation: Adapting to patient needs', February 2013, and the recent project undertaken by Charles River Associates on behalf of PhRMA. This takes a different approach by cataloguing examples of incremental innovation that have been aimed at addressing specific challenges in emerging markets.

11 This includes IFPMA reports 'Pharmaceutical R&D Projects to Discover Cures for Patients with Neglected Conditions' and 'Policies that encourage innovation in middle-income countries'.

interferes with the disease process at a molecular level can be described as 'radical innovations.' The discovery of closely related molecules with different attributes that may offer significant value in treating particular disease variants or patient segments can be referred to as 'incremental innovation'. This project is intended to cover the spectrum from incremental to radical.

Figure 6: Definitions of innovation and value



Source: CRA analysis

As also illustrated in Figure 6, medicines can deliver value in a number of different ways, including therapeutic and clinical benefits, quality of life benefits for patients and their families, and economic benefits in terms of using scarce healthcare resources more effectively or even bringing macro-economic benefits to the economy.

Given the objective of the project is to determine whether innovation in a number of key therapy areas has delivered value in MICs, we need to consider carefully the issue of causality. Obviously there is not a simple 'cause and effect' relationship between improving access to modern innovative medicines and an improvement in health outcomes and correlation does not mean that any improvement in health outcomes can be attributed to the evolution of new medicines. We have focused on studies that have test explicitly the role of new medicines, however given the number of quality studies testing these 'input-output' relationships in MICs are severely limited by lack of epidemiological and intervention databases, we have also attempted to show the chain of causality (for example, for medicines to deliver value, they need to be accessible, used in an appropriate treatment regime etc) and assembled a range of indirect evidence regarding the value they deliver.

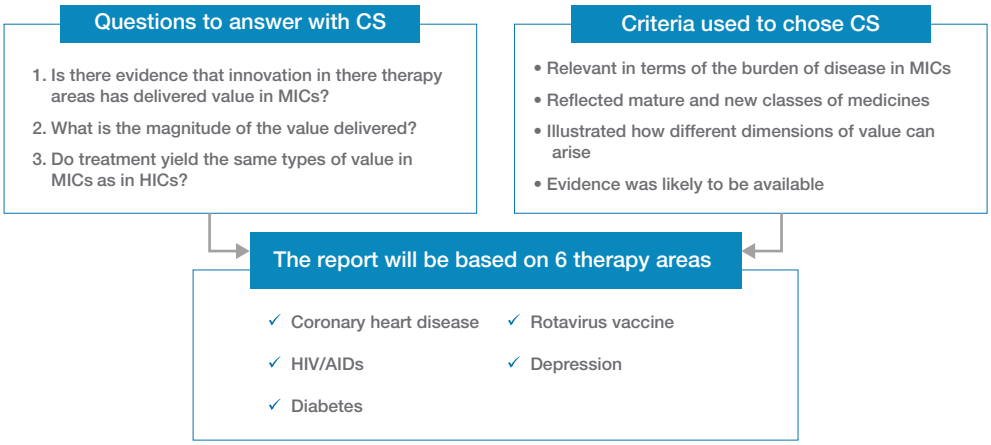
1.3. CHOICE OF CASE STUDIES AND APPROACH

The first issue to be addressed was the choice of the therapy areas and countries. It was important to choose therapy areas that are representative of the range of challenges faced by MICs. We have chosen a set of case studies such that they satisfy the following criteria:

- Therapy areas with particular importance to MICs
- A mix of communicable and non-communicable diseases (CDs and NCDs)
- Therapy areas where there is a mature class of medicines or where important new classes have been recently introduced

This criteria is illustrated in Figure 7.

Figure 7: Choice of case studies



Source: CRA analysis

Drawing on burden of disease data and taking into account the extent of available information and the quality of the evidence, we have focused on coronary heart disease (CHD), depression, diabetes type II, HIV/AIDs and rotavirus infections for the reasons below:

- CHD: More than 5 million people died as a result of CHD in 2008 in MICs. This represents 42% of all cardiovascular deaths (which numbered over 12 million). CHD is responsible for the loss of almost 30 million years of productive life, which represents 39% of the total DALYs lost due to CVD.
- Depression: Depression is the leading cause of disability globally in terms of total years lost due to disability.[12] A 2010 WHO study estimates that 151 million people suffer from depression globally.[13] Indeed, depression ranks as the seventh most important disease burden in LICs and MICs.[14] Marcus et al. suggest that by 2030, depression may be the highest contributor to burden of disease in the world.[15]
- Diabetes: Within MICs, diabetes was responsible for only 875,000 deaths, making up 3% of the total deaths from NCDs in MICs and for the loss of almost 16 million

12 Marcus et al (2012), 'Depression: a global public health concern', World Federation for Mental Health.

13 WHO (2010), 'Mental health and development: targeting people with mental health conditions as a vulnerable group'.

14 Patel et al (2007), 'Treatment and prevention of mental disorders in low-income and middle-income countries', The Lancet.

15 WHO (2010), 'Mental health and development: targeting people with mental health conditions as a vulnerable group'.

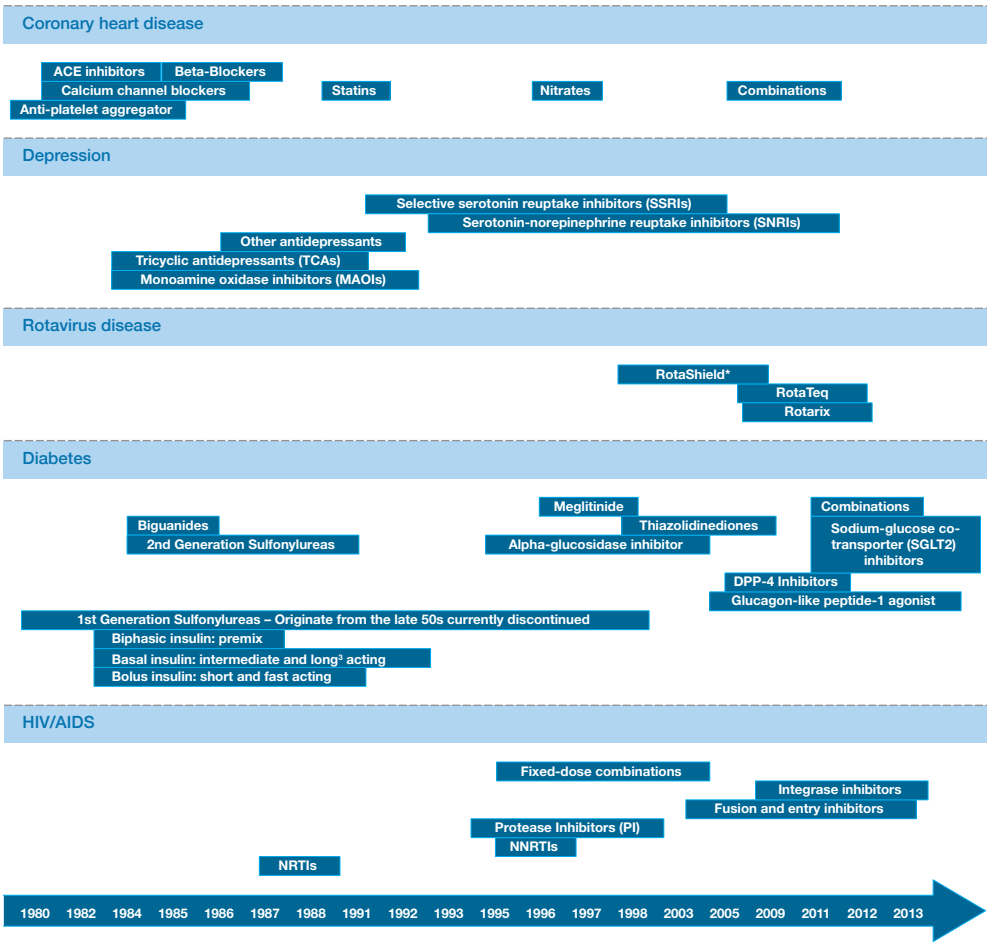
years of productive life in HICs in 2008. In addition, diabetes is clearly growing and of increasing concern.

- HIV: HIV represented a national crisis for many MICs. As HIV/AIDS is becoming a chronic disease (due to improvement in survival rates), the total population living with the disease is increasing. The overall global MIC population living with HIV/AIDS increased by around 34% between 2000 and 2011. In 2008, HIV/AIDS was responsible for 3% of deaths (excluding non-disease related mortality) representing 11% of all CD deaths in MICs.

- Rotavirus: Rotavirus caused more than a quarter of a million deaths among MICs and HICs in 2008 with the vast majority (all but 0.1%) of these deaths occur within MICs. The rotavirus mortality rates among children under 5 years old reached 5,213 per 100,000 children in LMICs in 2008, while the rate was 1,275 in UMICs and 85 in HICs.

And to reflect therapy areas that have mature and new classes of medicines (as illustrated in Figure 8 below.

Figure 8: Development of innovative treatment in the selected therapy areas



Source: CRA analysis

COUNTRY CHOICE

Given the significant differences between the therapy areas, we have taken quite different approaches to choosing the appropriate countries to include in the case studies. For example, for coronary heart disease (CHD) we looked at a range of MICs, whereas for rotavirus vaccine we compared a MIC to a HIC.

For **CHD** there is existing literature on benefits within developed economies. Several studies show how the use of treatment has benefited HICs in different ways. In developed countries, mortality rates due to CVD decreased substantially, often by more than 50%, over the last thirty years. This radical reduction in mortality rates correlates with the introduction of breakthrough therapies for CVD. There is significant evidence that these therapies influence both the disease prevalence rates and mortality.[16,17,18]

In addition to the clinical benefits,there is evidence that CHD treatments have reduced hospitalisation costs linked to physician and laboratory interventions.[19] For example, it has been shown that for every $24 spent on new medicines for CVD in OECD countries, $89 is saved in hospitalisation costs.[20,21] Finally, cardiovascular drugs have improved the quality of life of CHD sufferers.[22]

Much less attention has been given to the value that CHD treatments have brought in MICs. In order to see if similar benefits can be achieved in these markets, we have looked at Brazil, Russia, India, China and South Africa (BRICS), as these have a high disease burden of CHD and represent the largest fast-growing emerging economies.

For **rotavirus vaccine** we have focused on one HIC and one MIC that have included it in a national immunisation program. We chose Australia and Brazil as representatives of HICs and MICs respectively.

- Australia was one of the first countries to introduce a nationally funded rotavirus vaccination program and is still one of only a few developed economies that have done so.

- Brazil (along with a number of other countries in Latin America) was also among the first to implement routine vaccination against rotavirus and has the most comprehensive literature assessing the effect of the application of a rotavirus vaccine available.

16 Rayner and Petersen, 'European cardiovascular disease statistics: 2000 edition', British Heart Foundation Health Promotion Research Gorup, Oxford, 2000.

17 NERA (2004), 'The human and economic value of pharmaceutical innovation and opportunities for the NHS', a report for ABPI, May 2004.

18 Scandinavian Simvastatin Survival Study Group (1994), 'Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)', Lancet, 344, 1383–1389.

19 NERA (2004), 'The human and economic value of pharmaceutical innovation and opportunities for the NHS', a report for ABPI, May 2004.

20 Litchenberg (2009), 'Have newer cardiovascular drugs reduced hospitalization? Evidence from longitudinal country-level data on 20 OECD countries, 1995-2003', Health Economics, 15, 5.

21 A more specific example is discussed in Glick, et al (1995), 'Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial.

22 Glick, et al (1995), 'Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial.

1.4. THE STRUCTURE OF THE REPORT

The remainder of the report is structured around these five case. We follow the same approach for each of the studies:

- First, we look at the evolution of the treatment options for each therapy area and how these relate to the recommended first-line treatment in WHO guidelines.
- Second, we review the extent to which treatments are actually available and accessible within the selected markets.
- Third, we present the evidence available regarding the added value that treatment has brought to MICs.

The final chapter looks at the lessons we can draw from all five of the case studies and the policy implications.

2

CORONARY HEART DISEASE

Cardiovascular diseases (CVD) are one of the major causes of death within developing countries. Coronary heart disease (CHD) represents the largest proportion among all CVD. CHD leads to serious health consequences: as well as angina (chest pain), the main symptoms of CHD are heart attacks and heart failure.

In this chapter, we present a brief overview of treatment options for CHD within healthcare systems before turning to the question of whether these medicines have delivered value in different MICs.

2.1. EVOLUTION OF TREATMENT OPTIONS FOR CHD

To address the challenges of CHD, a range of different medicinal classes have been developed. In this section we will first look at the evolution of the treatment options for CHD and how these relate to the recommended first-line treatment for CHD in WHO guidelines.

THERAPY OPTIONS FOR THE TREATMENT OF CHD

The evolution of classes of drugs for CHD demonstrates a common pattern. The first in a class was often superseded by a series of additional medicines that were more efficacious or offered less severe side effects.[23] Figure 9 shows a summary of the first appearance of the main drug classes used to treat CHD:[24,25,26]

- **Antiplatelet aggregators** can help reduce the risk of a heart attack by thinning the patient's blood and preventing it from clotting. They have been used as primary and secondary treatment of CHDs since the US Food and Drug Administration (FDA) approval of Aspirin in the 1980s, and they are still widely used. Innovation in this class has continued actively over recent years with prasugrel and ticagrelor being introduced.

- **Beta-blockers** have a well-established place in the modern therapy of angina pectoris, hypertension and cardiac failure and were developed from the early 1960s through to the 1990s. Beta-blockers work by blocking the effects of a particular hormone in the patient's body, which results in a slower heartbeat and improved blood flow. The first beta-blocker to achieve some general utility was propranolol, which was licensed initially for angina. New beta-blockers (e.g. metoprolol) entered the market a decade later as a treatment for CHD. Advances in diagnostics and the understanding of congestive heart failure (CHF) during the 1980s and 1990s led to development of later beta-blockers, notably bisoprolol and carvedilol, which proved effective in treating CHF.

23 Sheridan and Attridge (2006), 'The impact of therapeutic reference pricing on innovation in cardiovascular medicine', Pharmacoeconomics, 24,2.

24 Sheridan and Attridge (2006), 'The impact of therapeutic reference pricing on innovation in cardiovascular medicine', Pharmacoeconomics, 24,2.

25 NHS choices, 'Coronary heart disease', last accessed May 2013, available here http://www.nhs.uk/Conditions/Coronary-heart-disease/Pages/Introduction.aspx

26 Other classes such as anticoagulants (e.g. warfarin) are also used for the treatment of diseases that are associated with coronary heart disease. In order to define the classes used for CHD we have followed the NHS recommendations. These are available here http://www.nhs.uk/Conditions/Coronary-heart-disease/Pages/Treatment.aspx

- **Calcium channel blockers** are widely used to treat hypertension. They decrease blood pressure by relaxing the muscles that make up the walls of the arteries. This causes the arteries to become wider, reducing the patient's blood pressure. The first calcium channel blocker was verapamil, which was discovered in the '60s but approved by the FDA in 1982. Verapamil still remains in use for the treatment of CHD, along with diltiazem, which also was approved in 1982 although it was developed a decade later than verapamil. The class evolved subsequently as a result of innovations to produce drugs that act selectively on the heart muscle with fewer side effects.

- **ACE (angiotensin converting enzyme) inhibitors** block the activity of a hormone called angiotensin II, which causes the blood vessels to narrow. As well as preventing the heart from working so hard, ACE inhibitors improve the flow of blood around the body. They have also been shown to reduce mortality in patients with chronic heart failure, and have had an important impact on the treatment of hypertension, particularly in diabetic patients and by preserving patients' left ventricular function following myocardial infarction. A large number of ACE inhibitors have been developed for the treatment of CHD.

- **Statins** are used to reduce the level of lipid deposits containing cholesterol as this is a major contributor to CHD. Lovastatin was the first statin approved by the FDA, in 1987. It was followed by several new molecules during the 1990s, and rosuvastatin, the most recent, was approved in 2003.

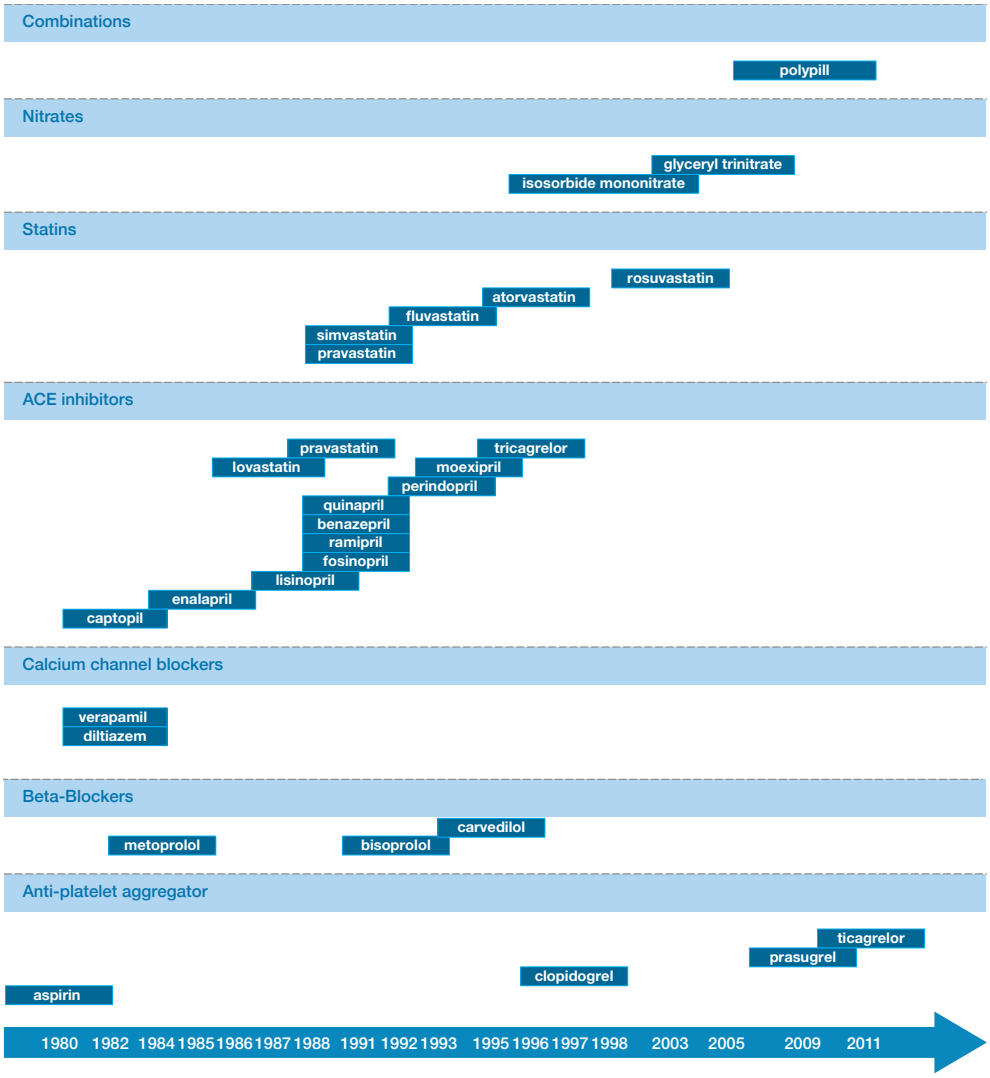
- **Nitrates** are used to widen the blood vessels. The first nitrate used for CVD was isosorbide mononitrate, approved by the FDA in 1998. A new nitrate, glyceryl trinitrate, was approved in 2005.

- The first **combination** of molecules to treat CVD was approved by the FDA in 2009. The polypill is a combination of a statin, aspirin and three blood pressure drugs, and it is expected to be used in secondary treatment of CVD.[27]

This evolution is illustrated Figure 9 below.

27 Lonn et al (2010), 'The polypill in the prevention of CVD: key concepts, current status, challenges and future directions', Circulation, 122.

Figure 9: First appearance of novel treatment classes for CHD



Source: CRA analysis

WHO GUIDELINES FOR FIRST-LINE TREATMENT FOR CHD

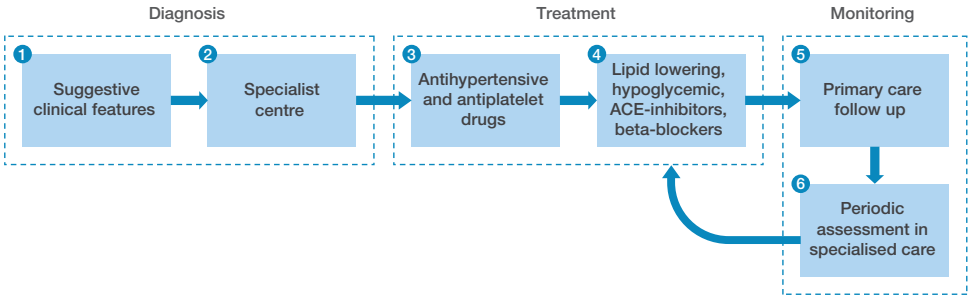
Diagnosis, treatment and management of CVD are very well defined within developed economies. In these markets, patients suffering from CVD are provided a clear treatment pathway. For example, a CVD patient in the UK National Health Service (NHS) is referred to primary or secondary care depending on the stage of his or her disease. When a patient suffers from an ischaemic cardiac attack, he is referred to secondary care, where he is treated until he is stabilised. Once CVD is established, the treatment is defined and monitored within primary care facilities. Long-term pharmacological treatment for patients who have suffered an attack includes aspirin, a beta-blocker and a high intensity statin. For secondary prevention of CVD, the UK NHS offers lipid modification therapy with a statin as well as blood-pressure-lowering therapy.

However, the management of CVD in general and CHD in particular within MICs typically lags behind that within developed markets. This is because, firstly, a large proportion of people with high cardiovascular risk remain undiagnosed and, secondly, even those diagnosed have insufficient access to treatment at the primary healthcare

level.[28] This situation reflects a lack of investment in infrastructure, equipment and human resources allocated to both the prevention and the management of CVD at the primary care level within these markets.[29] Also, at a central government policy level, little progress has been made in developing national clinical guidelines and distributing them as part of educational programmes for medical professionals.

The current WHO cardiovascular guidelines, which date from 2007, recommend patients see a specialist if they have experienced acute cardiovascular events, such as a heart attack, heart failure or angina, or if they suffer from hypertension or diabetes mellitus.[30] As shown in Figure 10, the doctor should treat all patients with antihypertensive and antiplatelet drugs and consider the use of lipid lowering drugs, hypoglycaemia drugs, ACE inhibitors or beta-blockers, depending on the patient profile.[31] Once the patient has been stabilised, he or she should be followed up in a primary care facility and will need periodic assessments in specialist care.

Figure 10: Patient pathway for the treatment of CVD, WHO recommendations



Source: CRA based on WHO guidelines

2.2. ACCESS TO MEDICINES FOR CHD

In order to ascertain the degree to which treatments for CHD have delivered these benefits in in MICs, it is useful to first determine if the current treatments are actually available and accessible in these markets.

Comparative evidence on access to CHD treatment is particularly limited both within and across MICs. Unlike therapy areas such as HIV, there is no dedicated international database that allows a global comparison of the accessibility of CHD treatment. To overcome this limitation we have looked at the following:

- If national strategies to fight against CVD have been applied within the selected countries
- Whether CHD medications have been included in essential drug lists (EDL) in particular markets

28 WHO (2011), 'Global atlas on cardiovascular disease prevention and control', A WHO, World Heart Federation (WHF) and World Stroke Organization (WSO) joint publication.

29 WHF (2010), 'State of the Heart. Cardiovascular disease report', World Heart Federation.

30 WHO guidelines also give recommendations for prevention of CVD in people with cardiovascular risk factors.

31 WHO (2007), 'Prevention of cardiovascular disease. Pocket guidelines for assessment and management of cardiovascular risk', WHO Publication.

- Direct statistical evidence on access to CHD within MICs
- The use of clinical guidelines on the treatment of CHD

NATIONAL STRATEGIES FOR CONTROLLING CVD

Although the burden of non-communicable diseases (NCDs), such as CVD, is rising within MICs, policymakers in many countries are only now starting to define national plans to fight against them. In particular:

- Brazil has developed a national plan to reduce the burden of NCD, which includes the prevention and treatment of CHD. The *Strategic Action Plan to Tackle Non-communicable Diseases (NCD) in Brazil, 2011-2022*, was defined by the Brazilian Ministry of Health (MoH). The Plan aims to prepare Brazil to contain the prevalence and limit the impact on society of these diseases over the next 10 years. The NCDs include stroke, heart attack, hypertension, cancer, diabetes and chronic respiratory diseases. Preventive policies include promoting healthy lifestyles and expanding access to pharmaceuticals, including free distribution of 15 key drugs for hypertension and diabetes.[32]

- The Russian Federation has not yet defined an official national strategy for the treatment of CHD or NCDs in general. However, at a UN assembly meeting in 2011 the Russian representative mentioned that the country was starting a project to implement the provisions of the Moscow declaration to monitor NCDs, control risk factors, and improve healthcare for people with NCDs through fostering international partnerships and cross-sectoral cooperation.[33] The Russian Federation introduced national guidelines for the prevention of CVD in 2011 with a 'Healthy Hearts' campaign to educate doctors through one-day courses in 23 Russian cities on the importance of prevention.[34]

- In China, the Ministry of Health, along with 15 departments of the Development and Reform Commission, signed the 'China National Plan for NCD Prevention and Treatment plan for 2012-2015'. The MoH is in the process of writing a specific action plan for CVD and diseases such as chronic obstructive pulmonary disease (COPD), cancer, and diabetes.[35]

- In India, the government has started taking measures towards prevention of heart disease especially among the rural population. The National Programme for Prevention and Control of Cancer, Diabetes, CVD and Stroke (NPCDCS) was introduced in July 2010 with a budget of more than $9 billion for interventions on diabetes and CVD. The NPCDCS aims to prevent and control common NCD through a) behaviour and lifestyle changes, b) providing early diagnosis and management

32 Brazilian Ministry of Health (2011), 'Strategic Action Plan to Tackle Noncommunicable Diseases (NCD) in Brazil, 2011-2022'.

33 United Nations (2011), 66th General Assembly GA/11146, available here http://www.un.org/News/Press/docs/2011/ga11146.doc.htm

34 Nainggolan (2011), 'Hope for a Russian revolution in CV prevention', Heart Wire, http://www.theheart.org/article/1211685.do, last accessed May 15, 2013.

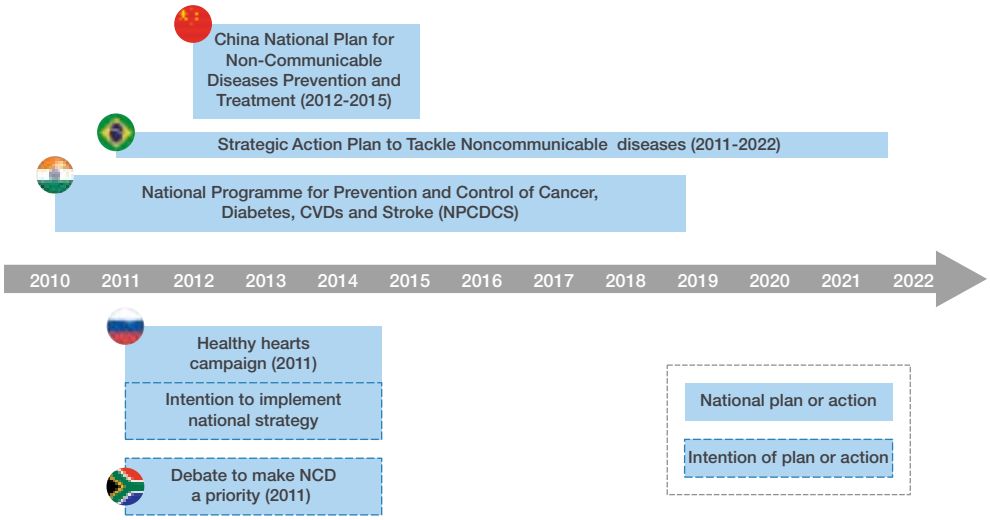
35 WHO (2013), 'CVD', WHO Representative Office China, http://www.wpro.who.int/china/mediacentre/factsheets/cvd/en/index.html, accessed May 15, 2013.

of common NCDs, c) building capacity within the healthcare sector, and d) establishing and developing capacity for palliative and rehabilitative care.[36]

- South Africa has focused the majority of public health efforts to fight communicable diseases (CDs). The Department of Health has not defined heart diseases as a policy priority. However, the debate over which non-communicable conditions should be prioritised is starting to increase.[37]

As illustrated in Figure 11, there are large differences between MICs; indeed, we found very little evidence of specific programmes in China, South Africa or India, where policy attention has largely focused upon CDs, maternity and childbirth.[38]

Figure 11: National strategies to fight against CVD within BRICS



Source: CRA analysis

THE INTRODUCTION OF CHD MEDICINES IN THE EDL

Another way to determine if medicines are generally available is to consider the essential drug list. Essential medicines, as defined by WHO, are 'those drugs that satisfy the healthcare needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford.'[39]

Each country is encouraged to define its own essential drug lists (EDL) and ensure the listed medicines are accessible to the population. Therefore, if a CHD drug is included on an EDL it is more likely that the population has access to that particular molecule.

36 Deloitte (2011), 'CVD in India. Challenges and way ahead', Research commissioned by ASSOCHAM India.

37 Freeman (2011), 'Should non-communicable conditions of high burden but low mortality be prioritised in South Africa?', Department of Health.

38 Gupta et al (2011), 'Translating evidence into policy for cardiovascular disease control in India', Health research policy and systems, 9,8.

39 WHO (2003), 'The selection and use of essential medicines', WHO technical report series, 914.

Box 1: The use of Essential Drug Lists within BRICS

Brazil has developed EDLs since 1964, but it was in 2005 that the list was reviewed by different stakeholders. The latest publication of RENAME (Relação Nacional de Medicamentos) was published in 2010.

The Russian market has used a Vital and Essential Drugs List (ZHNVLP) since 2010 as the base for the drug provision programme. The drugs included are mostly generic molecules with the exception of some oncology drugs and antiretrovirals.

The concept of essential medicines is relatively new to India. The first state to develop the essential medicine list was Tamil Nadu in 1994; however, it was Delhi that took the lead in developing a comprehensive Drug Policy in 1994 and was the only Indian state to have such a comprehensive policy.[40] The National List of Essential Medicines of India was revised in 2011, eight years after the previous revision. The NLEMI 2011 contains 348 medicines and was prepared over one and a half years by 87 experts.[41]

In China, the concept of a National Essential Medicine List (NEML) was first defined in 1979, with the first edition published in 1982. The first revision took place in 1996, which increased the number of drugs included. Since then the list has been reviewed every two years and has been used as a base for the selection of social health insurance medicines list.[42] The latest version, released in 2013, included cancer drugs.[43]

South Africa created the Essential Drug Programme (EDP) in 1996 as part of its National Drug Policy (NDP). Through the EDP, the NDP is designed to provide equal access for all South Africans. The EDP includes the Essential Medicines List, and the Standard Treatment Guidelines. South Africa outlines various commitments as part of the NDP objectives; these include ensuring availability and accessibility of essential medicines to all South African citizens; ensuring safety, efficacy and quality of medicines; ensuring good practice with regards to prescribing and dispensing medicines; promoting rational use of medicines through education, training, and information; and promoting the concept of individual responsibility for health.[44]

Source: CRA analysis from different sources

Within the BRICS we found that cardiovascular drugs have been included in their EDLs since the very early stage of their designby including at least one molecule for each therapeutic class. Differences within classes can be observed; for example, anti-platelets have been included since the late '90s, other classes, such as ACE inhibitors, were introduced later, as shown in Table 8.

40 Sitanshu et al. (2010), 'Concept of Essential medicines and Rational Use in Public Health', Indian journal of community medicine, 35,1.

41 Manikandan and Gitanjali (2012), 'National list of essential medicines of India: The way forward', Journal of postgraduate medicine, 58, 1.

42 Wang and Zhang (2011), 'The selection of essential medicines in China: progress and the way forward', Southern medicines review, 4,1.

43 HIS Global Insights (2013), 'China issues revised 520-drug NEDL, includes cancer drugs, paediatric formulations', 18th March. Available at http://www.ihs.com/products/global-insight/industry-economic-report.aspx?id=1065977333

44 South Africa Department of Health, Essential Drugs Programme (EDP) website: http://www.doh.gov.za/health-topicsor.php?t=Essential%20Drugs%20Programme%20(EDP).

Table 8: Year of introduction of treatment classes used for the treatment of CHD in BRICS

	BRAZIL	RUSSIAN FEDERATION	INDIA	CHINA	SOUTH AFRICA
ACE inhibitors	2002	2010	2003	2002	2012°
Beta-blockers	2007	2010	2003	2002	1998
Antiplatelets	1998	2010	2003	2002	1998
Statins	2002	2010	N/A	2002	2012°
Nitrates	2002	2010	2003	2002*	1998
Calcium channel blockers	2002	2010	2003	2002	1998

Source: CRA analysis. Note: °EDLs in South Africa are publicly available only for 1998 and 2012

THE EXISTING EVIDENCE ON ACCESS TO CHD WITHIN MICS

International organisations, such as WHO, and academic researchers have developed surveys to determine the extent to which cardiovascular drugs are used for the treatment of CHD within MICs.

Use of cardiovascular drugs in MICs

Recent reviews have compared access in HICs to access in MICs. In a broad view it was observed that the proportion of people not receiving cardiovascular drugs in HICs (11.2%) is much lower than in upper-middle-income countries (UMICs) (45.1%) and lower-middle-income countries (LMICs) (69.3%).[45]

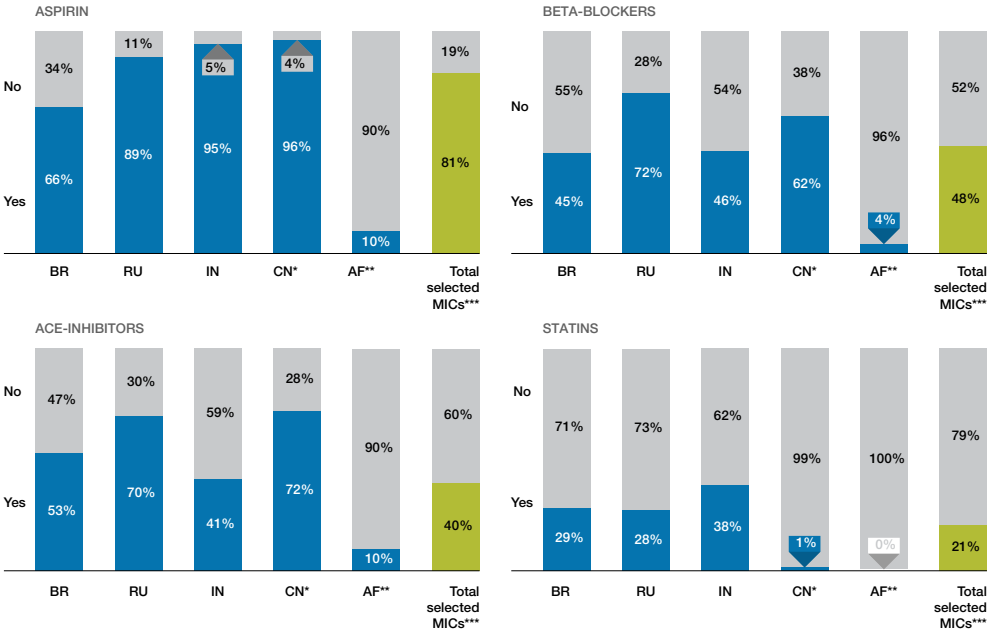
WHO developed a six-month cross-sectional survey of CHD patients within 10 MICs to understand how secondary prevention of CHD works in MICs.[46] Combining the WHO study with academic reviews we can see that the most common cardiovascular drug used was aspirin (81.2%), followed by beta-blockers (48.1%). ACE inhibitors were used by 39.8%, while statins were used by only 20.8%.[47] Significant differences appear to exist between the selected countries with regard to their use of CHD medications, with Russia leading the use of ACE inhibitors, China the use of aspirins and India of statins. This is shown in Figure 12.

45 Yusuf, et al. (2011), 'Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey', The Lancet, 278, 9798.

46 The study included Brazil, Egypt, India, Indonesia, Islamic Republic of Iran, Pakistan, Russian Federation, Sri Lanka, Tunisia and Turkey.

47 Mendis et al (2005), 'WHO study on prevention of recurrences of myocardial infarction and stroke WHO-PREMISE', Bulletin of WHO, 83,11.

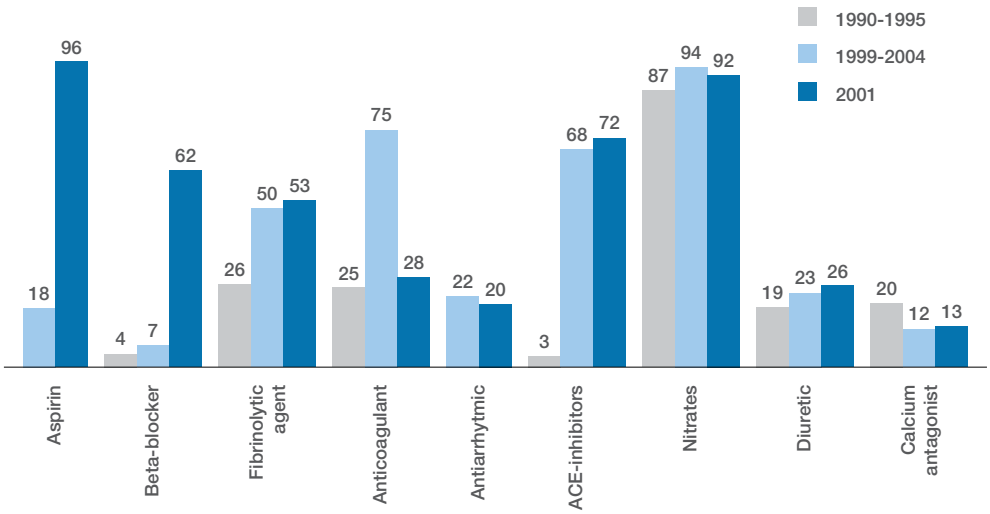
Figure 12: Use of medications in patients with CHD by country (% of total patients)



Source: CRA analysis from different sources.[48] Note: China (CN), Brazil (BR), Russian Federation (RU), India (IN), Africa (AF); **AF includes South Africa and Zimbabwe; ***MICs included: Brazil, Egypt, India, Indonesia, Islamic Republic of Iran, Pakistan, Russian Federation, Sri Lanka, Tunisia and Turkey

Patient management has also changed over time as innovative treatments have become more available within MICs. Looking at the patterns and trends of drug prescriptions for acute myocardial infarction in China, we can see in Figure 13 that more patients have been prescribed aspirin, ACE inhibitors and beta-blockers in recent years.

Figure 13: Pattern and trends of drug prescription for patients with acute myocardial infarction in China (% of the surveyed ACI patients)



Source: Zhang et al. (2008), 'Coronary heart disease in China', Heart, 94

48 For Brazil, Russia, India and total MICs we use Mendis et al (2005), 'WHO study on prevention of recurrences of myocardial infarction and stroke WHO-PREMISE', Bulletin of WHO, 83,11; Africa includes both South Africa and Zimbabwe and we use Yusuf, et al. (2011), 'Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey', The Lancet, 278, 9798; Chinese data comes from different sources *Zhang et al. (2008), 'Coronary heart disease in China', Heart, 94* for aspirin, beta-blockers and Ace inhibitors and Yusuf et al (2011) for statins.

The use of cardiovascular treatment guidelines within MICs

As mentioned above, cardiovascular treatment guidelines are not common in MICs; indeed, countries like China and India do not yet have guideline recommendations for the treatment of CVD.[49] However, some countries, such as the Russian Federation, have recently introduced treatment recommendations, while others, such as India, have plans to define protocols to be implemented within the next years. Indeed, the Indian Health Ministry has finalised the norms for clinical and surgical intervention in CVDs. It is the first of the 20 disciplines for which standard treatment guidelines (STGs) are being drawn up.[50]

The Russian Federation's national guidelines for the prevention of CVD, introduced in 2011, cover recommendations to decrease risk factors as well as secondary prevention through drug therapy. The medicines mentioned were antiplatelet drugs, anticoagulants, beta-blockers and ACE inhibitors, as well as activators of ATP-sensitive potassium channels. As mentioned above, the government developed a 'Healthy Hearts' campaign to educate doctors about prevention of CVD. Additionally, Russians can attend one of 500 policlinics in the country for a free 50-minute consultation for an assessment of CVD risk factors.[51]

In South Africa, official treatment guidelines have existed since 1998, when the National Department of Health released the first edition of the 'Standard treatment guidelines and essential drug list'. The guidelines detail the recommended treatment for specific diseases. For the treatment of CHD, the guidelines suggest the use of beta-blockers, such as atenolol, ACE-inhibitors, such as ramipril, and/or calcium channel blockers, such as verapamil.

2.3. THE VALUE OF TREATMENT FOR CHD

Finally, in this section we look at the evidence on the value that treatment for CHD has brought to MICs and try to determine the extent to which any improvement in health outcome can be associated to access to innovative medicines. As described above, obviously there is not a simple 'cause and effect' relationship between improving access to modern innovative medicines and an improvement in health outcomes.

THERAPEUTIC/CLINICAL BENEFITS

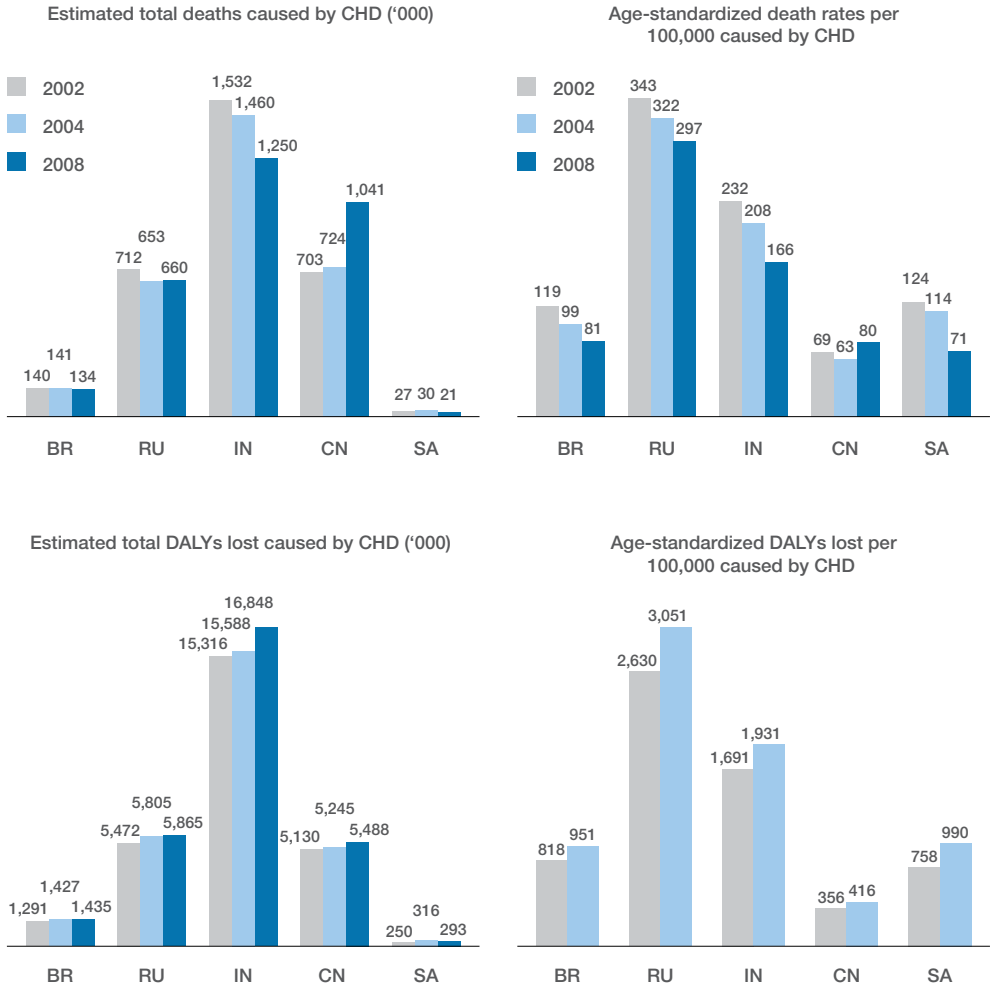
Overall mortality rates associated with CHD have decreased significantly over the past decade within all the selected countries. As Figure 14 shows, BRICS have seen a reduction in the number of people dying from CHD over the period 2002-2008. Only in China has the burden increased slightly. With regard to the number of DALYs lost, a rise on the burden can be observed in all countries.

49 Huffman (2011), 'Coronary heart diseases in India', Center for Chronic Disease Control; Zhao and Hu (2012), 'Barriers to translating EU and US CVD guidelines into practice in China', Nat Rev Cardiol 9(7): 425-429.

50 The Indian Express (2013), 'Health Ministry finalises treatment protocol for CVD', March 4.

51 Nainggolan (2011), 'Hope for a Russian revolution in CV prevention', Heart Wire, http://www.theheart.org/article/1211685.do, last accessed May 15, 2013.

Figure 14: Burden of CHD within BRICS



Source: CRA analysis using WHO Statistical Information System (WHOSIS), Global burden of disease. Available here http://www.who.int/healthinfo/global_burden_disease/gbd/en/index.html Last accessed: July 2013. Note: CHD – coronary heart disease, BR – Brazil, RU – Russia, IN – India, CN – China, SA – South Africa

However, although this is clearly consistent with greater access to innovative medicines, there appears little obvious correlation between the reduction in mortality and the levels of access to CHD medicines.

Even so, there is common agreement that a reduction in the burden of CHD within these markets is correlated to improvements in the access to CHD treatment. Recent WHO work concludes that if people at risk of developing myocardial infarctions and strokes can be identified, and measures taken to reduce their cardiovascular risk, the vast majority of fatal and non-fatal cardiovascular events can be prevented. It also concludes that primary care access to cardiovascular risk assessment and essential medicines for reducing cardiovascular risk can improve health outcomes of people with hypertension.[52]

A positive relationship between the use of cardiovascular drugs and the reduction of mortality rates in MICs has been demonstrated by several recent expert studies:

52 WHO (2011), 'Global atlas on cardiovascular disease prevention and control', A WHO, WHF and WSO joint publication.

- WHO developed a study looking at mortality from CHD and stroke over a 10-year period across 38 countries. This Multinational Monitoring of Trends and Determinants of CVD initiative (WHO MONICA Project) showed that the decline in mortality has been attributed to reduced incidence rates, but also to improved survival after cardiovascular events due to prevention and treatment interventions.[53]

- A recent review of literature on cardiovascular interventions within LICs and MICs showed that the available high level of evidence supports a wide range of interventions for the prevention of CVD as being cost-effective across all world regions.[54] In particular, drugs to lower 'high' blood pressure were found to be in the 'very cost-effective' or 'cost-effective' range in all studies. Analyses on the use of statins, on the other hand, produced mixed results: three studies reported that they were cost-effective while two others found that they were not.[55] However, overall, cardiovascular drugs were found to bring clinical benefits to developing economies and also to be cost-effective in those markets.

- Policy initiatives for control of CVD in India, which include both primary and secondary prevention, have been suggested, but evidence of efficacy has emerged only recently. These initiatives, it is claimed, will have an immediate impact in reducing morbidity and mortality.[56] This is consistent with a recent report that showed there has been rapid growth in the use of drugs that manage early risk factors in India (e.g. ACE inhibitors and statins), which has helped significantly reduce cardiac-disease-related mortality.[57]

Finally, there are the results from clinical trials where the effectiveness of medicines for CHD has been shown in Brazil[58,59], China[60,61], South Africa.[62]

53 WHO(2003), 'MONICA. Monograph and multimedia source book. World's largest study of heart disease, stroke, risk factors, and population trends 1979-2002', WHO MONICA Project.

54 The authors found 16 studies that reviewed cardiovascular interventions within lower – or middle-income countries. They used WHO cost-effectiveness definitions, based on *x times the GNI per capita* and added a 'very cost effective' category to assess the results of the papers.

55 Shroufi, et al (2013), 'Cost effective interventions for the prevention of cardiovascular disease in low and middle income countries: a systematic review', British medical journal Public health, 13, 285.

56 Gupta et al (2011), 'Translating evidence into policy for cardiovascular disease control in India', Health research policy and systems, 9,8.

57 Deloitte (2011), 'Cardiovascular diseases in India. Challenges and way ahead', Research commissioned by ASSOCHAM India.

58 Serrano et al (2010), 'Lack of Clopidogrel-Statin Interaction in Patients Undergoing Coronary Stent Implantation', Arquivos brasileiros de cardiologia, 95,3.

59 Araujo et al (2007), 'Cost-effectiveness and budget impact analysis of rosuvastatin and atorvastatin for LDL-cholesterol and cardiovascular events lowering within the SUS scenario', International Journal of Atherosclerosis, 2,3.

60 Zhang et al (2008), 'The effect of pre-hospital statins therapy on incidence of in-hospital death and total MACCE in patients with PCI', Journal of Clinical Pharmacy and Therapeutics, 33,6.

61 COMMIT (2005), 'Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial', The Lancet, 366, 9497; 'Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial', The Lancet, 366.

62 Ridker et al (2008), 'JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein', New England Journal of Medicine, 359.

COSTS IN HEALTHCARE SYSTEMS

Using retrospective studies of the cost-effectiveness of various forms of drug interventions in specific clinical settings as a basis for informing future policy directions, to optimise value for money in allocating scarce funds, is in its infancy in most MICs, primarily due to lack of data, researchers and funds.

Currently, because of the limited local primary care facilities in most countries, the vast majority of patients who get access to modern CVD medicines do so from ambulatory (outpatient) hospital clinics.[63] However, there is a broad acceptance in policy terms that extending such access through public health funding will, over the longer term, limit the cost burden on hospitals of undertaking acute crisis interventions as the disease progresses. This result is illustrated by an Argentinian study (although not a case study country) which shows that the number of hospitalisations due to angina revascularisations was reduced by 36% to 43% as result of treatment with beta-blockers, statins or antiplatelet agents. The number of myocardial revascularisations was reduced by 21% to 23% as result of treatment with beta-blockers, statins or antiplatelet agents.[64]

In a more broadly based analysis, the American Heart Association showed that in addition to the loss of life associated with CVD, MICs face economic challenges linked to the growth in CVD to epidemic proportions, as they have limited funds and other resources.[65]

WIDER BENEFITS TO SOCIETY

It is worth highlighting that CVD affects adults of working age and therefore potentially has a wider economic impact. [66] This may include an impact on economic productivity and long term social services costs. A report on the burden of CVD in Brazil, India, China, South Africa and Russia estimated that 21 million years of future productive life were lost because of CVD each year, as shown in Figure 15.[67] India has the most life years lost, whilst the cost in Russia is highest per 100,000 of population.

63 One of the few studies illustrating the costs of the disease is in South Africa. This shows that in 1991, 25% of the South African total healthcare expenditure (public and private) was devoted to the treatment of CVD. Pestana et al (1995), 'The direct and indirect costs of cardiovascular disease in South Africa in 1991', South African Medical Journal, 86,6.

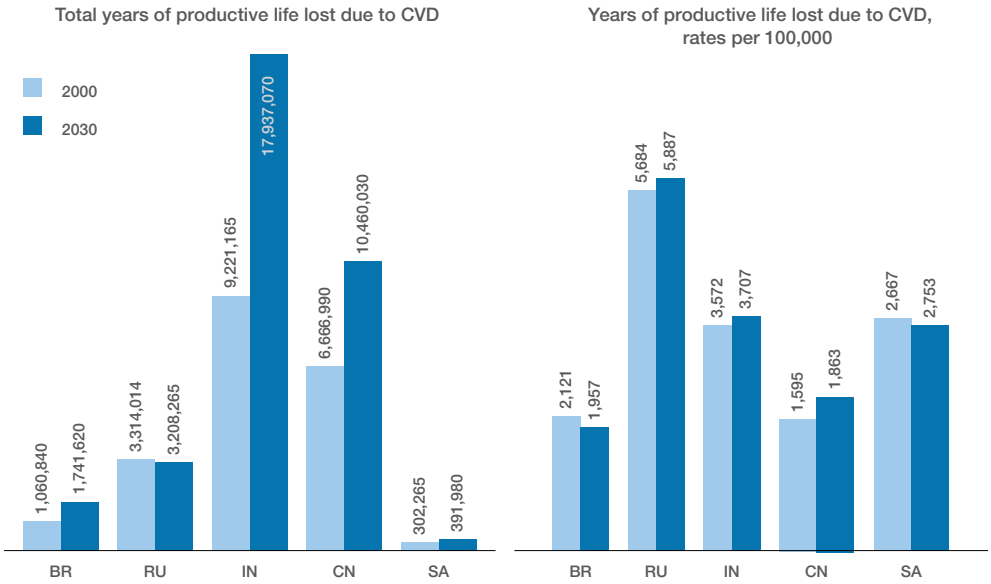
64 Rubinstein et al (2010), 'Estimation of the burden of cardiovascular disease attributable to modifiable risk factors and cost-effectiveness analysis of preventative interventions to reduce this burden in Argentina'.

65 Gariziano (2005), 'Cardiovascular diseases in the developing world', Circulation, 112.

66 Gariziano (2005), 'Cardiovascular diseases in the developing world', Circulation, 112.

67 Leeder, et al. (2005), 'Race against time. The challenge of cardiovascular disease in developing economies', The Center for Global Health and Economic Development.

Figure 15: Years of productive life lost due to CVD, total and rates per 100,000, 2000 and 2030



Source: Leeder, et al. (2005), 'Race against time. The challenge of cardiovascular disease in developing economies', The center for global health and economic development

Further major improvements in extending access to modern medicines for CVD could reduce the productivity losses from CHD, both by helping CHD patients to return to work and by reducing the probability of their premature death before retirement age. However, convincing evidence regarding these productivity benefits from the case study countries is scarce.

2.4. THE VALUE OF MEDICINES FOR CHD IN MICS

CHD is a major issue in terms of mortality and years of life lost due to premature death and disability. WHO statistics show that within MICs more than 5 million people died as a result of the disease in 2008.

Despite this massive burden of disease it is only in recent years, within the context of broader initiatives to tackle NCDs, that national strategies to reduce the burden of CHD have been proposed and to some limited degree implemented. Looking at selected MICs, only Brazil, India and China have a national plan, and even these were started only within the last three years. Therefore is still relatively early to assess their impacts. In many cases, most notably in India, these plans have been subject to delays, due to lack of funds and bureaucratic issues.

In terms of access, all the selected countries have included at least one molecule in each class in their EDL, which in principle means that the molecules should be widely available to the population. However, this depends on adequate primary care capabilities to diagnose, treat and monitor patients. Only Russia and South Africa have specific guidelines for the treatment of CHD. Looking at the existing evidence within the selected countries, we found that use of cardiovascular drugs varies substantially from country to country. Molecules that have been in the market for many years and

are inexpensive, such as aspirin, are widely used in most countries, whereas statins, which are relatively more expensive and require laboratory testing facilities to test cholesterol levels before an appropriate drug and dosage level is selected, are less commonly used, despite the strong evidence for their effectiveness and increasingly high levels of uptake in developed countries.

The evidence that the treatment for CHD has brought clinical and therapeutic benefits within the BRICS is mixed. With the exception of China, CHD-caused mortality rates decreased between 2002 and 2008 in all the selected countries, however, given the lack of any correlation between access and reduced mortality, it is difficult to attribute this directly to access to medicines. On the other hand, it is clearly the case that clinical research has shown the efficacy of these products in these markets. There is also country-specific evidence from some case study countries and international evidence that an improvement in access to CHD treatment would lead to a further reduction in the burden of CHD. As yet, only limited evidence exists showing the link between the use of cardiovascular drugs and other benefits, such as cost savings or wider socio-economic gains such as labour productivity and lower social care costs.

Taking the above into consideration, and given the burden of the disease in MICs as well as the nature of cardiovascular drugs, there appears a significant untapped opportunity for further health gains from the more widespread deployment of these innovative medicines from past decades. Table 9 summarises the main findings of the CHD study.

Table 9: Summary of the findings related to treatment, usage and value of medicines for CHD within BRICS

	BRAZIL	RUSSIA	INDIA	CHINA	SOUTH AFRICA
National strategy against CVD	NCD plan 2011-2022	N/A some efforts started	NCD plan 2010	NCD plan 2012-2015	N/A
Inclusion in EDL	Yes	Yes	Yes except statins	Yes	Yes
Use of CVD drugs*	48%	65%	55%	58%	No reliable estimate
Existence of treatment guidelines	No	Yes	To be implemented	No	Yes
Evidence on the value of treatment	Clinical	Clinical	Clinical	Clinical	Clinical

Source: CRA analysis; *Calculated using the average use of the selected drugs in Figure 12

3

DEPRESSION

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. At its worst, depression can lead to suicide.

In this chapter, we provide a brief overview of treatment options within healthcare systems before turning to the question of whether these medicines have delivered value in different MICs.

3.1. EVOLUTION OF TREATMENT OPTIONS FOR DEPRESSION

In this section we will first look at the evolution of the treatment options for depression and how these treatments relate to the recommended first-line treatment for depression in WHO guidelines.

THERAPY OPTIONS FOR THE TREATMENT OF DEPRESSION

There are several classes of antidepressants with different mechanisms of action. All antidepressants are similarly effective in treating moderate to severe depression, but they differ in terms of adverse effects.[68]

More specifically, there are two generations of antidepressants: the first generation, which includes Monoamine oxidase inhibitors (MAOIs) and Tricyclic antidepressants (TCAs), and the second generation, which includes selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The main differentiating factors are the more tolerable side effects of second-generation antidepressants.[69] Fluoxetine was the first second-generation antidepressant and is regarded as representing radical innovation within depression treatment. After this, the new molecules developed within the second generation of antidepressants are commonly regarded as representing different forms of incremental innovation.

The timeline of the main classes of antidepressants is shown in Figure 16:

- **Monoamine oxidase inhibitors (MAOIs)** were among the earliest treatments for depression, with products on the market since the 1950s, and signified a radical innovation in treating depression. Prior to MAOIs, only psychotherapy or physical treatments such as electroconvulsive therapy, which were more expensive and less acceptable to the patients and their families, were available for treating depression.[70] However, MAOIs can cause serious interactions.[71] Iproniazid was the first MAOI introduced, and selegiline is one of the newer molecules approved.

68 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

69 AHQR (2011), 'Second-generation antidepressants in the pharmacologic treatment of adult depression: an update of the 2007 comparative effectiveness review'.

70 Nutt and Attridge (2013), 'CNS drug development in Europe – Past progress and future challenges', Neurobiol Dis. 2013.

71 WebMD, 'Depression Medicines', http://www.webmd.com/depression/guide/optimizing-depression-medicines

- **Tricyclic antidepressants (TCAs)** were developed almost concurrently to MAOIs and had better activity-to-side-effect profiles.[72] Side effects include stomach upset, dizziness, dry mouth, changes in blood pressure, changes in blood sugar levels, and nausea. However, some meta-analysis of trials showed that they are not effective in children and adolescents.[73] Examples of TCAs are imipramine, amitriptyline, and clomipramine.

- **Selective serotonin reuptake inhibitors (SSRIs)** were launched in the mid to late 1980s, although some were launched in the last few years. This generation of antidepressants are often the first-line treatment for depression as they are exceptionally safe.[74] Side effects are generally mild, and include upset stomach, sexual problems, fatigue, dizziness, insomnia, weight change, and headaches. While the positive effects were comparable to the older medicines, the risks of serious side effects were much lower.[75] Examples of SSRIs are fluoxetine and sertraline.

- **Serotonin and norepinephrine reuptake inhibitors (SNRIs)** are a newer class of antidepressants that developed after 1990, and there are fewer molecules in this class. They represent a significant improvement in terms of safety in overdose and tolerability of adverse effects.[76] Side effects include upset stomach, insomnia, sexual problems, anxiety, dizziness, and fatigue. Examples of SNRIs arevenlafaxine and duloxetine.

There are other antidepressants that do not fit into the above classes but are still used for the treatment of depression or as add-on therapies.

72 Nutt and Attridge (2013), 'CNS drug development in Europe – Past progress and future challenges', Neurobiol Dis. 2013.

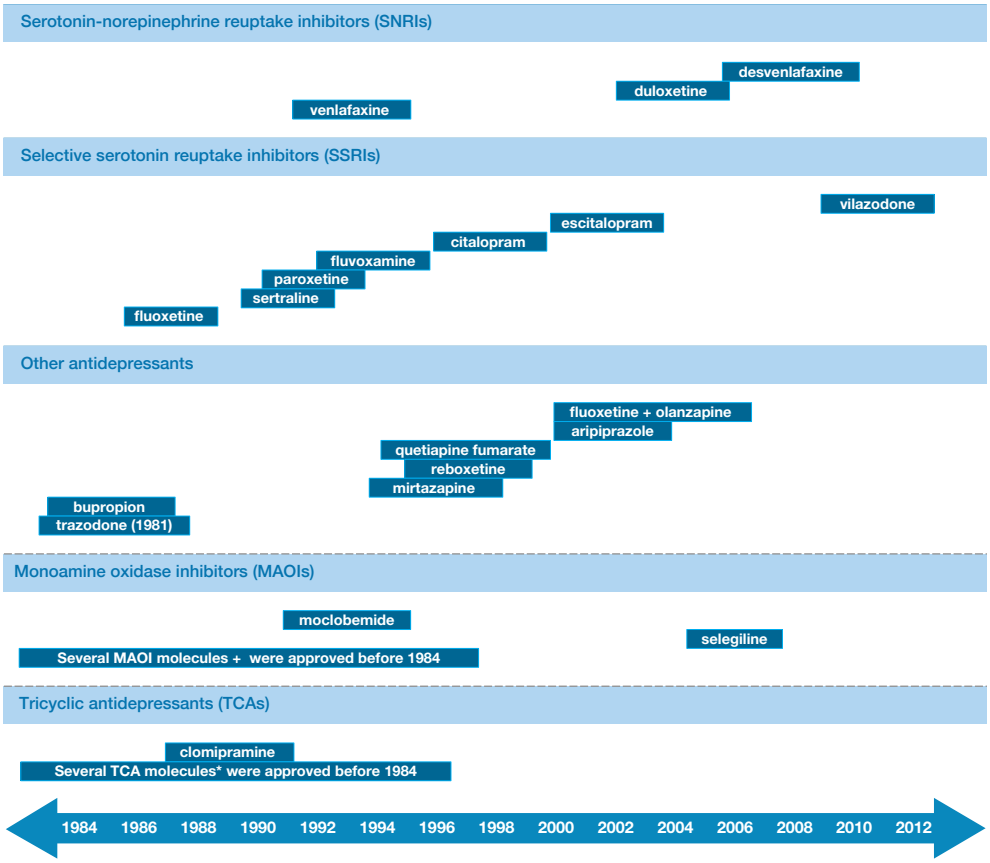
73 Klasen and Crombag (2013), 'What works where? A systematic review of child and adolescent mental health interventions for low and middle income countries', Soc Psychiatry Psychiatr Epidemiol 48: 595-611.

74 Nutt and Attridge (2013), 'CNS drug development in Europe – Past progress and future challenges', Neurobiol Dis. 2013.

75 IFPMA (2012), 'Mental and neurological disorders: innovative therapies, innovative collaborations'.

76 Nutt and Attridge (2013), 'CNS drug development in Europe – Past progress and future challenges', Neurobiol Dis. 2013.

Figure 16: First appearance of novel treatment classes for depression



Source: CRA analysis. Note: TCAs approved before 1984 include: imipramine (1959), amitriptyline (1961), nortriptyline (1964), desipramine (1964), protriptyline (1967), doxepin (1969), dothiepin/dosulepin (1969), mianserin (1976), trimipramine (1979), lofepramine (1983); MOAIs approved before 1984 include: isocarboxazid (1959), tranylcypromine (1961), phenelzine (1961)

WHO GUIDELINES FOR FIRST-LINE TREATMENT FOR DEPRESSION

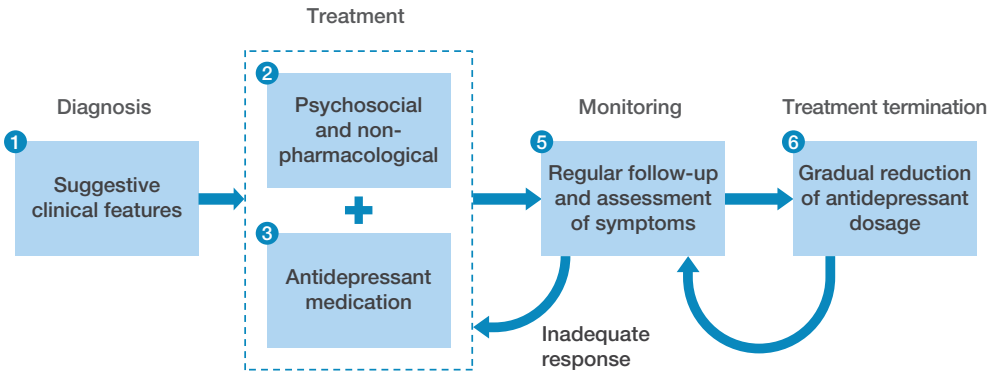
Depression is a disorder that can be diagnosed and treated in primary care. However, this requires that primary care doctors receive special training to diagnose and treat the disease and they have assistance from a specialist.[77] As outlined in the WHO Mental Health Gap Action Programme (mhGAP) guideline, preferable treatment options consist of basic psychosocial support combined with antidepressant medication or psychotherapy, such as cognitive behaviour therapy, interpersonal psychotherapy or problem-solving treatment. Antidepressants can be a very effective form of treatment for moderate to severe depression but are not the first line of treatment for cases of mild or sub-threshold depression. As an adjunct to care by specialists or primary healthcare providers, self-help is an important approach for helping people with depression.[78]

77 McDaid et al (2008), 'Barriers in the mind: promoting an economic case for mental health in low – and middle-income countries', World Psychiatry 7: 79-86.

78 Non-pharmacological treatment includes providing education about depression for the sufferer and his or her family, offering the person an opportunity to talk and addressing the psychosocial stressors, reactivating the sufferer's social networks, prescribing structured physical activities, and scheduling follow-up appointments with a healthcare provider. Marcus et al (2012), 'Depression: a global public health concern', World Federation for Mental Health.

For moderate and severe depression, WHO mhGAP recommends non-pharmacological and pharmacological treatment (see Figure 17).[79] However, such methods are extremely labour intensive.

Figure 17: WHO treatment recommendation for depression



Source: WHO (2010), 'mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings'

WHO recommends SSRIs for those who are considering self-harm, the elderly, and people with CVD. Fluoxetine is recommended for adolescents over 12. Patients on SSRIs with marked or prolonged restlessness are recommended to be switched to TCAs or concomitant use of diazepam, a sedative, for a brief period. If patients have inadequate response after four to six weeks on medication, the dosage can be increased. If symptoms still persist four to six weeks after the maximum dose was prescribed, a medication switch can be considered. When the patient has no or minimal depressive symptoms for nine months to a year, the antidepressant can be terminated by gradually reducing the medication dose.[80]

3.2. ACCESS TO MEDICINES FOR DEPRESSION

Comparable evidence on access to antidepressants is particularly limited within MICs but to overcome this, as we did for CHD, we have looked if national strategies to fight against depression have been applied within the selected countries, whether antidepressants have been included in EDLs in particular markets, direct evidence on access to antidepressants within MICs and the use of clinical guidelines on the treatment of depression.

NATIONAL STRATEGIES FOR DEPRESSION

Most of the BRIC countries have a national mental health strategy, although none have one that specifically addresses depression. That said, we note that there are complex overlapping disease states in mental health that make it difficult to separate out depression as a stand-alone category.[81] Most of the mental health policies are focused more on improving

79 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

80 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

81 Nutt and Attridge (2013), 'CNS drug development in Europe – Past progress and future challenges', Neurobiol Dis. 2013.

the healthcare infrastructure as it relates to mental health. Only Chile (which was chosen for this reason) has a fairly comprehensive strategy for depression compared to the BRIC countries. Several measures have been applied within the selected countries:

- Brazil's mental health policy was formulated in 1991 and updated in 2005. The main aims were to decentralise care of mental health patients. The public Unified Health System (SUS) also allows free access to a variety of mental health services and essential antidepressants, although the reach in remote areas is uncertain. Brazil has also started some innovative services and interventions such as the Psychosocial Community Centres (CAPS) and the Return Home program.[82] However, there does not seem to be any strategy directed specifically at depression.

- China's first National Mental Health Plan (2002-2010) was signed in April 2002, and in August 2004 a Proposal on Further Strengthening Mental Health Work was approved and served as the de facto mental health policy. However, thus far there are only programs for psychoses such as schizophrenia, bipolar disorder, delusional disorder, and schizoaffective disorder.[83] On May 1, 2013, China's first Mental Health Law came into effect. The law is expected to ensure treatment for mental health regardless of the patient's ability to pay.[84] Depression is identified in the National Health Policy of China as a chronic disease that should be managed in primary care settings.[85] However, there does not seem to be a national strategy directed at depression in China.

- Chile stands out against the other MICs (and was chosen for that reason). It has the National Depression Detection and Treatment Program (PNDTD), a well-established primary care program that was introduced in 2001 and became the national program in 2003. PNDTD includes identification of depression, treatment, and closely monitored follow-up for enrolled cases and functions within primary care, which consists of a network of over 500 primary care centres.[86] Additionally, depression among adults, defined as those over 15 years old, was listed as one of the 56 prioritised diseases under the Universal Access with Explicit Guarantees (AUGE) plan in 2006.[87] The legislation established a guaranteed basic, uniform benefit plan that applied equally to those covered by the National Health Fund public insurance system (FONASA), which accounts for 69% of the population, and the private insurance system ISAPREs, which accounts for 17% of the population.[88]

- India launched the National Mental Health Programme (NMHP) in 1982 to prevent and treat mental and neurological disorders. The strategies of the NMHP and the District Mental Health Programme (DMHP) focus on improving the structural

82 WHO-AIMS (2007), 'Mental health system in Brazil'.

83 Liu et al (2011), 'Mental health system in China: history, recent service reform and future challenges', World Psychiatry 10: 210-216.

84 Zhang (2013), 'China: Mental Health Law takes effect on May 1', Library of Congress, http://www.loc.gov/lawweb/servlet/lloc_news?disp3_l205403562_text

85 Chen et al (2011), 'Depression care management for late-life depression in China primary care: protocol for a randomized controlled trial', Trials 12: 121.

86 Araya et al (2012), 'Lessons from scaling up a depression treatment program in primary care in Chile', Rev Panam Salud Publica 32(3); 234-240.

87 UHC Forward, 'Compare: Benefits package', available at http://uhcforward.org/reforms/compare/benefits/229,139,15, accessed June 27, 2013.

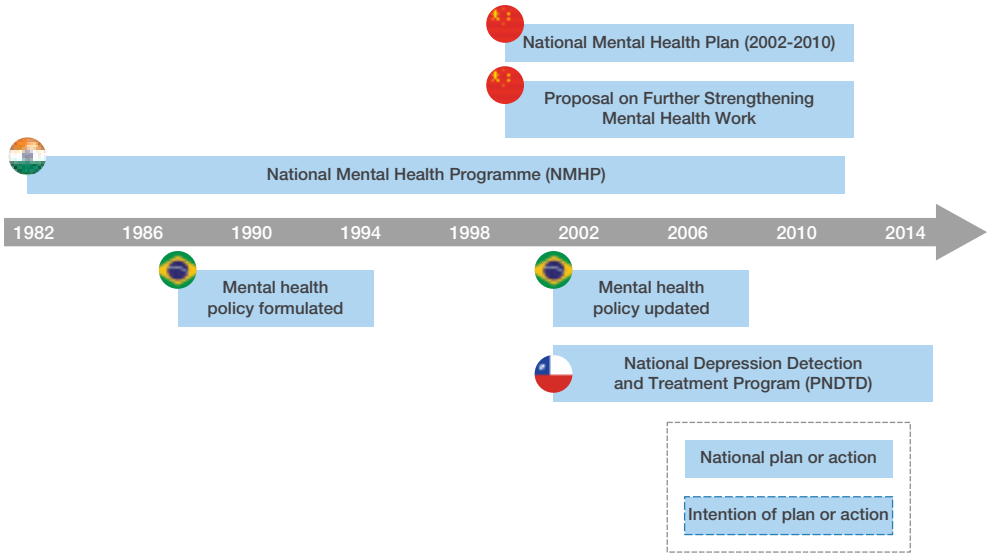
88 Vargas and Poblete (2008), 'Health prioritization: the case of Chile', Health Affairs 27(3): 782-792.

aspects of the healthcare system and disseminating information regarding mental health. It was noted that mental health professionals were not actively involved in or aware of the program, and there was poor commitment to this program from the government, health professionals and community.[89] However, there are signs that the program may be under a revival. The budget allocation for the NMHP increased from Rs. 280 million in the Ninth Five-Year Plan to Rs. 1390 million in the Tenth Five-Year Plan, and the budget for the NMHP in the Eleventh Five-Year Plan (2007-2012) was Rs. 10,000 million. The focus of the NMHP in the Eleventh Five-Year Plan was on increasing the number of mental health providers and centres.[90]

- The Russian federal health ministry develops strategies and policy guidance for mental health, which are then used by the regional governments to develop local strategies.[91] However, the focus of mental health issues in Russia seems to be on psychiatric care rather than depression, as resource allocation tends to favour large inpatient institutions, which are less beneficial to depression sufferers.[92] Mental health issues are predominantly treated by psychiatrists rather than in the primary care or community setting, which is where depression patients often receive treatment in other countries.[93]

The timeline for these national strategies is set out in Figure 18 below.

Figure 18: Timeline for the introduction of national strategies to address depression in BRIC + Chile



Source: CRA analysis. Note – it is unclear when the Russian Ministry of Health started developing strategies for mental health

89 National Institute of Health and Family Welfare, 'National Mental Health Programme', http://www.nihfw.org/NDC/DocumentationServices/NationalHealthProgramme/NATIONALMENTALHEALTHPROGRAMME.html

90 Sinha and Kaur (2011), 'National mental health programme: manpower development scheme of eleventh five-year plan', India J Psychiatry 53(3): 261-265.

91 Jenkins et al (2007), 'Mental health reform in the Russia Federation; an integrated approach to achieve social inclusion and recovery', WHO Bulletin 85(1): 821-900.

92 McDaid et al (2006), 'Health system factors impacting on delivery of mental health services in Russia: multi-methods study', Health Policy 79(2-3): 144-152.

93 Jenkins et al (2007), 'Mental health reform in the Russia Federation; an integrated approach to achieve social inclusion and recovery', WHO Bulletin 85(1): 821-900.

THE INTRODUCTION OF ANTIDEPRESSANTS IN EDLS

Amitriptyline and fluoxetine are included in the WHO EDL for treating depression.[94] Amitriptyline was included in the WHO adult EDL before 2002, while fluoxetine was introduced in 2007.[95]

As can be observed in Table 10, the EDLs of BRIC and Chile include medicines from at least two classes of antidepressants. TCAs and SSRIs are on the EDL in all of these countries. China has the most generous national drug list inclusion policy, as at least one of the medicines in each class was included. In addition to inclusion on the Chinese EDL, SNRIs were also included on the Chilean drug list while MAOIs were also included on the Brazilian one. Fluoxetine was on the national EDL of all countries before it was included on the WHO adult EDL except for Russia, where we had only the 2012 EDL and were not able to confirm the timing of fluoxetine's addition. Amitriptyline was also included in all EDLs, but the available records do not go back far enough for us to determine whether it was included in the national EDLs before inclusion in WHO EDLs.

Table 10: Years antidepressant classes were introduced to the EDL in BRIC + Chile

	BRAZIL	RUSSIAN FEDERATION	INDIA	CHINA	CHILE
Tricyclic antidepressants (TCAs)	2000	2012	2003	2002	2005
Monoamine oxidase inhibitors (MAOIs)	2002	N/A	N/A	2002	N/A
Selective serotonin reuptake inhibitors (SSRIs)	2002	2012	2003	2002	2005
Serotonin norepinephrine reuptake inhibitors (SNRIs)	N/A	N/A	N/A	2002	2005
Other	2007	N/A	N/A	2002	2005

Source: CRA analysis based on publicly available national EDLs. Note – the second portion of the 2010 Russia EDL was not available

EVIDENCE ON ACCESS TO ANTIDEPRESSANTS IN MICS

Given the lack of international data we have examined country-specific evidence on use, where it is available, to determine the level of antidepressant use in the case study countries.

94 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

95 WHO (2002), 'WHO model list (revised April 2002): 12th edition'; WHO (2007), 'WHO model list of essential medicines, 15th list'.

Use of antidepressants in MICs

As with other diseases in MICs, large numbers of depression sufferers go undiagnosed and untreated, and this is confirmed by a study conducted across several cities, two of which were Porto Alegre, Brazil, and St. Petersburg, Russia. The study found that only 11% of 155 depression sufferers in Porto Alegre received some kind of antidepressant treatment after their primary care physicians were notified of the diagnosis. Of those receiving antidepressants, 91% received an effective dose. None of the 115 depression sufferers in St. Petersburg, Russia received antidepressant treatment after their primary care physicians were notified of the diagnosis, the lowest treatment rate of all the studied cities. In Porto Alegre, 17% of the patients received some kind of treatment for their depression, while in St. Petersburg only 3% received some kind of treatment. In both cities, treatment unaffordability was the most frequently mentioned barrier to treatment. Cost was cited as the barrier to receiving treatment by 40% of patients in Porto Alegre and 75% of patients in St. Petersburg.[96] Indeed, nearly 90% of those suffering from depression in China fail to get proper treatment due to worries about discrimination and to a lack of professional psychiatrists.[97] Another study found that only 8% of people with mood disorders in China saw healthcare professionals for their illness.[98] A paper examined the treatment prevalence of mental disorders found that only 8% of patients with depression receive treatment in low and middle income countries.[99]

However, there is some evidence of availability and the types of products that are available:

- A WHO Assessment Instrument for Mental Health Systems (WHO-AIMS) study found that in Brazil, at least one antidepressant is available in all outpatient mental health facilities and 21% to 50% of physician-based primary healthcare clinics.[100] A further study of antidepressant prescriptions filled in Belo Horizonte's Civil Servants' Clinic pharmacy (Brazil), which has 4,000 registered patients (depressed and non-depressed), found that 712 prescriptions for antidepressants were filled in 2005, of which 652 were included in the study. Of these prescriptions, 57% were for SSRIs and 31% were for tricyclic antidepressants, where fluoxetine was the most commonly prescribed antidepressant (28% of prescriptions), and nortriptyline was the most frequently prescribed among tricyclic antidepressants (14% of prescriptions). However, most of the prescriptions (78%) originated from the private healthcare system, which is relatively difficult to access rather than the public system and commercial pharmacies.[101]

- The Indian Psychiatric Society evaluated antidepressant prescription patterns of 706 patients with first-episode depression in 16 centres across India, one of the

96 Simon et al (2004), 'Prevalence and predictors of depression treatment in an international primary care study', Am J Psychiatry 161:9.

97 Xinhua News Agency (2007), '90% of depression sufferers fail to get proper treatment', www.china.org.cn/health/2007-05/19/content_1211317.htm

98 Zhang (2010), 'Major depressive disorder treatment guidelines in China', J Clin Psychiatry 71: e06.

99 Academy of Medical Sciences (2008), "Challenges and priorities for global mental health research in low- and middle-income countries".

100 WHO-AIMS (2007), 'Mental health system in Brazil'.

101 Hurtado et al (2010), 'Factors associated to antidepressant prescription for civil servants of Belo Horizonte, MG', Brazilian Journal of Pharmaceutical Sciences 46(2).

few multi-centre antidepressant utilisation studies conducted in the country. The study found that escitalopram was the most commonly prescribed antidepressant (40% of total prescriptions), followed by sertraline (17.6%) and fluoxetine (16.3%). SSRIs accounted for 79.2% of all antidepressant prescriptions, followed by TCAs (15.15%) and SNRIs (11.3%). The study found that the preferred antidepressant molecules varies depending on the treatment centre.[102] This is confirmed by other centre-specific studies done in India. For example, a study of 170 patients who attended psychiatric outpatient clinics in a hospital in Pondicherry, India, in 2006, and received antidepressants, found that duloxetine accounted for 56.5% of prescriptions, followed by escitalopram (25.3% of prescriptions) and mirtazapine (19.4% of prescriptions).[103]

- A WHO-AIMS study found that the availability of at least one antidepressant depends on the type of health centre in Hunan, China: at least one antidepressant is available in 100% of community-based psychiatric inpatient units, 94% of mental hospitals, 91% of mental health outpatient facilities, 51% to 80% of physician-based primary healthcare clinics, and less than 20% of non-physician-based primary healthcare clinics.[104]

- A cross-national study of patients treated with antidepressants in psychiatric centres in five East Asian countries found that 56% of patients in China receiving antidepressants in this setting have mood disorders, which includes depression. Overall, SSRIs were the most commonly prescribed antidepressant (57.6% of prescriptions), followed by TCAs (17.2%). The most commonly prescribed 'older' antidepressants in China are amitriptyline, clomipramine and maprotiline, while the most commonly prescribed 'modern' antidepressants were fluoxetine, paroxetine and sertraline.[105] The study found that across the five psychiatric centres in China, fluoxetine was the most frequently prescribed antidepressant (33%), followed by paroxetine.[106] In a further study in China, although TCAs are recommended second-line after other antidepressants, they are typically used first line due to the lower cost and greater availability compared to newer antidepressants.[107]

We have also looked specifically at the situation in Chile. In 2005, 20% of depression cases received treatment through the FONASA public health system. However, in 2008, three years after AUGE was introduced, 34% of depression cases received treatment, signifying a 70% increase in coverage in three years. Hospitalisation due to depression also increased by 26% between 2000 and 2006, according to research, this demonstrates not that the system failed to treat depression but that the AUGE reforms eased the demand constraint by offering better financial coverage and thus

102 Grover et al (2013), 'IPS multicentric study: antidepressant prescription patterns', Indian J Psychiatry 55(1): 41-45.

103 Lahon et al (2011), 'A retrospective drug utilization study of antidepressants in the psychiatric unit of a tertiary care hospital', Journal of Clinical and Diagnostic Research 5(5): 1069-1075.

104 WHO-AIMS (2006), 'Mental health system in Hunan province of the People's Republic of China'.

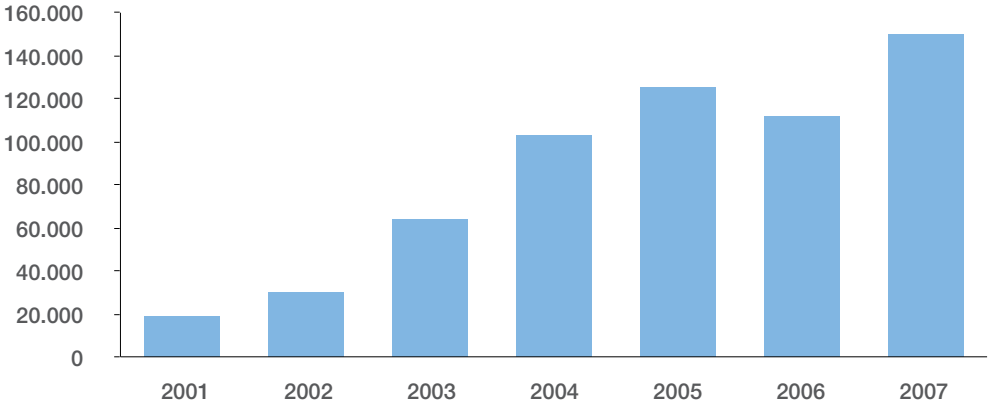
105 Sim et al (2007), 'Newer antidepressant drug use in East Asian psychiatric treatment settings; REAP (Research on East Asia Psychotropic Prescriptions) Study', Br J Clin Pharmacol 63(4): 431-437.

106 Uchida et al (2007), 'International study on antidepressant prescription pattern at 20 teaching hospitals and major psychiatric institutions in East Asia: Analysis of 1898 cases from China, Japan, Korea, Singapore and Taiwan', Psychiatry and clinical Neurosciences 61: 522-528.

107 Zhang (2010), 'Major depressive disorder treatment guidelines in China', J Clin Psychiatry 71: e06.

improving access to diagnosis and treatment of depression.[108] Indeed, depression was the fourth most common disease covered by AUGE, and accounted for 7% of total AUGE cases from AUGE's inception until 2011.[109] Depression accounted for 8% of AUGE's cost.[110] As demonstrated in Figure 19, PNDTD has been growing steadily since its inception, and the budget for PNDTD reached US$6 million in 2005.[111] However, a survey found that lack of information was the largest reason AUGE benefits were not used.[112]

Figure 19: Number of people receiving treatment through the National Depression Detection and Treatment Program (PNDTD) in primary care, Chile, 2001-2007



Source: Araya et al (2012), 'Lessons from scaling up a depression treatment program in primary care in Chile', Rev Panam Salud Publica 32(3); 234-240

The use of treatment guidelines for depression within BRIC + Chile

Brazil, India, China and Chile all have national treatment guidelines for mental health, usually drawn up by a medical association. There do not appear to be national guidelines for mental health in Russia.

The Brazilian Medical Association reviewed four guidelines published in 2003 by international, British and American associations to develop treatment guidelines for depression in Brazil. Antidepressants are recommended first line for moderate to severe depression and dysthymia, are not recommended for mild depression, and can be considered for all other cases. SSRIs are recommended as having the best clinical profile, although mirtazapine, reboxetine, and venlafaxine were also recommended, and TCAs or venlafaxine were recommended for severe depression in hospitalised patients. Treatment should be evaluated after four weeks, and if there is only partial

108 Bitran et al (2010), 'After Chile's health reform: increase in coverage and access, decline in hospitalisation and death rates', Health Affairs 29(12).

109 Paraje and Vasquez (2012), 'Health equity in an unequal country: the use of medical services in Chile', International Journal for Equity in Health 11(81).

110 Bossert (2009), 'Priority setting for health insurance plans', presentation.

111 Araya et al (2012), 'Lessons from scaling up a depression treatment program in primary care in Chile', Rev Panam Salud Publica 32(3); 234-240.

112 World Bank (2008), 'Chile: Regime of explicit health guarantees (Plan AUGE)', from 'Realizing rights through social guarantees: an analysis of new approaches to social policy in Latin America and South Africa'.

response after four or six weeks of treatment, the physician can either increase the dose, change the class of antidepressants, or switch to MAOI in patients with atypical side effects from the original antidepressants. The Brazilian guidelines also make recommendations regarding continuing, maintaining and discontinuing treatment.[113]

The Indian Psychiatric Society established clinical guidelines for the treatment of depression in India. Antidepressants are recommended for use in patients with mild, moderate and severe depression. SSRIs, TCAs, mirtazapine, bupropion and venlafaxine are recommended as likely to be optimal agents for most patients. TCAs such as imipramine and amitriptyline are not recommended for certain patients, such as those with cardiovascular conditions. Treatment should be evaluated after six to eight weeks, after which adjustment to treatment can be made and evaluated again after six to eight weeks to determine if the new regimen should be continued or adjusted. The guidelines also discuss the use of guidelines for continuing, maintaining and discontinuing antidepressant treatment.[114]

The Chinese Society of Psychiatry and National Centre for Mental Health published the Chinese Guideline for Prevention and Treatment of Mental Disorders: Depressive Disorder in 2007. The guidelines recommend patients start on an SSRI, an SNRI, or a noradrenergic and specific serotonergic antidepressant (NaSSA) after being diagnosed with major depressive disorder. Patients who do not achieve sufficient response can switch to TCAs or add on another antidepressant or mood stabiliser.[115]

Finally, the Chilean Ministry of Health has issued depression guidelines as part of the PNDTD. The guidelines recommend treating the depressed patient using a combination of psychotherapy and pharmacological treatments. The guide recommends the use of SSRIs, TCAs and anti-anxiety agents. The Ministry of Health does not specify which molecule to use in each class of treatment options.[116]

3.3. THE VALUE OF TREATMENT FOR DEPRESSION

Finally, in this section we look at the evidence on the value that treatment of depression has brought to MICs.

THERAPEUTIC/CLINICAL BENEFITS

As Figure 20 shows, while the total number of deaths due to depression in Brazil and India increased between 2002 and 2008, the age-standardised death rate generally decreased except in Brazil. The total DALYs lost due to depression remained relatively constant in the case study countries, with the exception of India where there seems to be a slight increase.

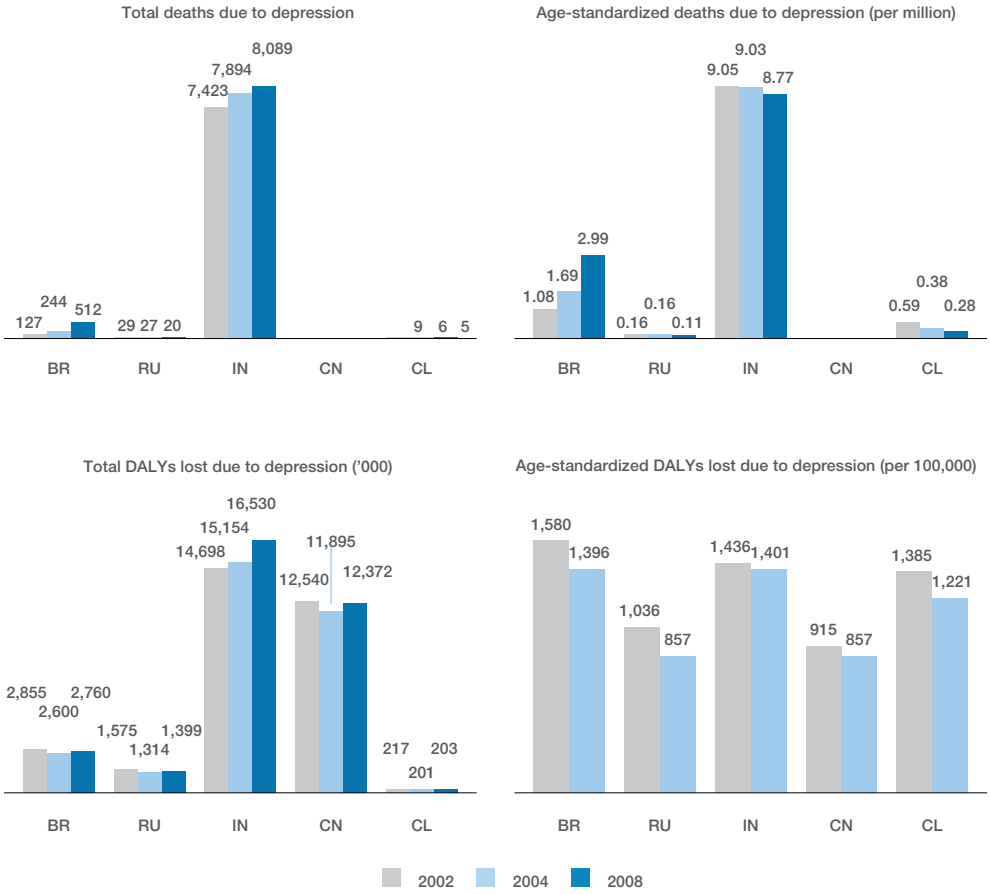
113 Fleck et al (2009), 'Review of the guidelines of the Brazilian Medical Association for the treatment of depression', Rev Bras Psiquiatr 31(Suppl): S7-17.

114 Gautam et al (2005), 'Clinical practice guidelines for the management of depression', Indian Psychiatric Society, http://www.indianjpsychiatry.org/cpg/cpg2004/CPG-PsyInd_13.pdf

115 Zhang (2010), 'Major depressive disorder treatment guidelines in China', J Clin Psychiatry 71: e06.

116 Ministerio de Salud (2006), 'Tratamiento de personas con depresion', Gobierno de Chile, Junio 2006.

Figure 20: Burden of depression in BRIC + Chile



Source: CRA analysis using WHO (2011), Burden of disease data. Note: BR – Brazil, RU – Russia, IN – India, CN – China, CL – Chile.
Note: There were no deaths due to depression reported in China

The evidence on the clinical efficacy of antidepressants in MICs is not as extensive as that of HICs. However, the evidence available suggests that antidepressants are just as effective in MICs, which have more disadvantaged patient populations or under-resourced systems of care compared to HICs.[117] That said, the value of antidepressants, as reflected in clinical trials results, is difficult to measure because of the high placebo effect and the difficulty of physically measuring improvements in depression.[118]

The most compelling evidence comes from Chile, where there have been a number of studies. Between 2000 and 2006, the case-fatality rate for patients admitted into the health system for depression treatment dropped by 98.6%, possibly because depression was added to the AUGE list of priority diseases and patients received treatment as a result of this reform.[119] A trial among 240 depressed women was conducted in the primary care setting. The randomised controlled trial (RCT) found that a multi-component stepped-care programme, including group psychoeducation for all suffers and antidepressants—fluoxetine (SSRI), amitriptyline (TCA) or imipramine (TCA)—for

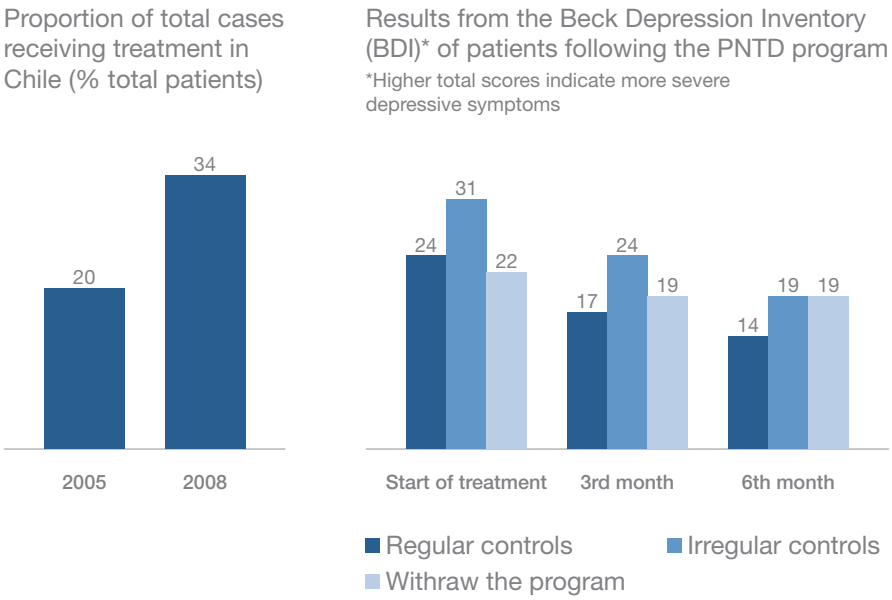
117 Patel et al (2009), 'Packages of care for depression in low – and middle-income countries', PLoS Medicine 6(10); Patel et al (2007), 'Treatment and prevention of mental disorders in low-income and middle-income countries', The Lancet.

118 Mukherjee (2012), 'Post-Prozac nation: the science and history of treating depression', New York Times.

119 Bitran et al (2010), 'After Chile's health reform: increase in coverage and access, decline in hospitalisation and death rates', Health Affairs 29(12).

the more severe sufferers, resulted in 70% of the sample recovered at six months compared to 30% in usual care. Those in the RCT were more likely to receive medication, and in more appropriate doses for longer periods of time, than those in usual care (79% of women in the stepped-care group received antidepressants compared to 34% in the usual-care group).

Figure 21: Improved clinical outcomes in Chile



Source: Bitran et al (2010), "After Chile's health reform: increase in coverage and access, decline in hospitalization and death rates", Health Affairs 29(12): 2161-2170; Alvarado and Rojas (2011), "El programa nacional para el diagnóstico y tratamiento de depresión en atención primaria: una evaluación necesaria", Revista Médica de Chile, 139

However, it is important to note that the authors attribute the improved clinical outcomes to the stepped-care programme as a whole rather than specifically antidepressants, as adjusting for medication did not alter the findings of improved outcomes under stepped-care.[120]

A further study assessed the effectiveness of the PNDTD program among 162 women in seven centres across the country. The study found that the depressed patients who completed the six-month treatment experienced a reduced level of depression and scored better on the SF-36 quality of life questionnaire. However, the study again does not isolate the effect of the pharmacological treatments.[121] Finally, evidence assessing the Chilean program supported the evidence provided by Araya et al (2003) in their study that followed up a larger sample of the population using the program once they have finished the six-month treatment. The authors showed that patients who finished the program experienced improvements in their clinical profile.[122]

120 Araya et al (2003), 'Treating depression in primary care in low-income women in Santiago, Chile: a randomised controlled trial', Lancet 361: 995-1000.

121 Antini and Alvarado (2008), 'Mejoría de la calidad de vida en personas atendidas en el 'Programa para la Detección, Diagnóstico y Tratamiento Integral de la Depresión en Atención Primaria', en Chile', Revista Psiquiatría Uruguay, 72,2.

122 Alvarado and Rojas (2011), 'El programa nacional para el diagnóstico y tratamiento de depresión en atención primaria: una evaluación necesaria', Revista Médica de Chile, 139.

There are even fewer studies of the effects of antidepressant use on healthcare spending among depression sufferers. Generally, studies tend to focus on the cost of depression treatment rather than compare it to the cost when there is no treatment. Only one study examined the effect of antidepressant use on healthcare cost compared to placebo.

- Simon et al (2002) examined the outpatient and total health services costs of people with depression of different severity levels in Porto Alegre, Brazil, and St. Petersburg, Russia. All patients with depression had lower outpatient and total health-service costs nine months into the study compared to baseline, regardless of their depression's severity level and whether they were treated for it. The reduction in total health services costs was the largest for those in remission in both Brazil and Russia compared to those with partial remission or persistent depression. However, the results were statistically insignificant and inconclusive.[123]

- A study looking at the cost-effectiveness of SNRIs, SSRIs and TCAs in the treatment of major depressive disorder from the Brazilian Ministry of Health's viewpoint found that introducing SNRIs into the formulary had a 52% probability of generating savings of 1% of the total budget. SSRIs and TCAs are already included in the Brazilian formulary.[124]

- Depression in India was associated with significantly higher healthcare costs, lost-time costs and risk of catastrophic health expenditure (defined as 10% or more of monthly household income spent on healthcare), when depressed women were compared to women not suffering from depression, even after controlling for age, literacy and other disorders. The authors hypothesise that patients often complain only of the somatic symptoms, and as a result their depression goes untreated and they are often treated with unnecessary medication, thus increasing their risk for catastrophic health expenditure, although it is possible that depression was caused by the catastrophic health expenditure.[125] This finding suggests that the cost of depression to the household could decrease if patients receive better diagnosis and treatment. Another study of 450 patients in Goa found that fluoxetine, an SSRI, reduced healthcare costs in the short and long term (2 months vs. 2 to 12 months) compared to placebo and was more cost-effective. It would cost 100 rupees more to get the same health improvement on a placebo as an antidepressant.[126]

- In Chile, savings from using AUGE reach up to 1 million pesos for patients with severe depression.[127] The AUGE programme was estimated to have saved US$339 per

123 Simon et al (2002), 'Course of depression, health service costs, and work productivity in an international primary care study', Gen Hosp Psychiatry 24(5): 328-335.

124 Machado et al (2007), 'The economic impact of introducing serotonin-noradrenaline reuptake inhibitors into the Brazilian national drug formulary: cost-effectiveness and budget-impact analyses', Pharmacoeconomics 25(11): 979-990.

125 Patel et al (2007), 'Prioritizing health problems in women in developing countries: comparing the financial burden of reproductive tract infections, anaemia and depressive disorders in a community survey in India', Tropical Medicine and International Health 12(1):130-139.

126 Patel et al (2003), 'Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: a randomised, controlled trial', The Lancet 361.

127 World Bank (2008), 'Chile: Regime of explicit health guarantees (Plan AUGE)', from 'Realizing rights through social guarantees: an analysis of new approaches to social policy in Latin America and South Africa'.

patient in annual out-of-pocket spending for health problems due to depression.[128] An analysis of the stepped-care program of Araya et al (2003), which includes psychosocial therapy and antidepressant therapy in the more severe sufferers, versus usual care, found both interventions to be cost-effective. The incremental cost per quality-adjusted life-years (QALY) gained—the incremental cost-effectiveness ratio (ICER)—for the stepped-care programme was I$468 (international dollars) per QALY, while the ICER for usual care was I$113 per QALY. The Chilean GDP per capita, which is often used as the threshold for cost-effectiveness, in 2003 was I$9,900, making both the stepped-care program and usual care cost-effective.[129]

WIDER BENEFITS TO SOCIETY

It is generally recognised that poverty and mental illness, which includes depression, interact in a negative cycle. The stressful conditions of living in poverty put people at higher risk of developing a mental illness. At the same time, people with mental health conditions are sometimes unable to work because of their symptoms, or they are required to spend money on the treatment of their mental healthcare. Paying for mental healthcare may worsen the sufferer's financial and health standing if the care given is ineffective or inappropriate.[130]

Despite the relationship between mental illness and poverty, few studies have been conducted outside of HICs that examine the wider economic cost of depression to society.[131] Additionally, the studies rarely examined the societal benefits of antidepressant use compared to untreated depression. However, those with milder depression seem to lose less productivity compared to those with more severe depression. Since interventions with antidepressants are considered cost-effective and, when used correctly, can improve the patient's condition, it is likely that antidepressants can also bring wider benefits to society in the MICs.

- As a proxy of how treatment would bring about benefits, we can examine the difference in functional impairment measured by the length of time since the last major depressive episode (MDE). As shown in the therapeutic benefits section, if antidepressants can reduce the severity of the depression, then one can infer that use of antidepressants can bring about a similar level of functionality as that of someone who suffered depression in the past but not recently. As shown in Figure 22, the longer the time from a person's last MDE, the lower his or her functional impairment. This was true in Brazil and China, although India was a slight anomaly.

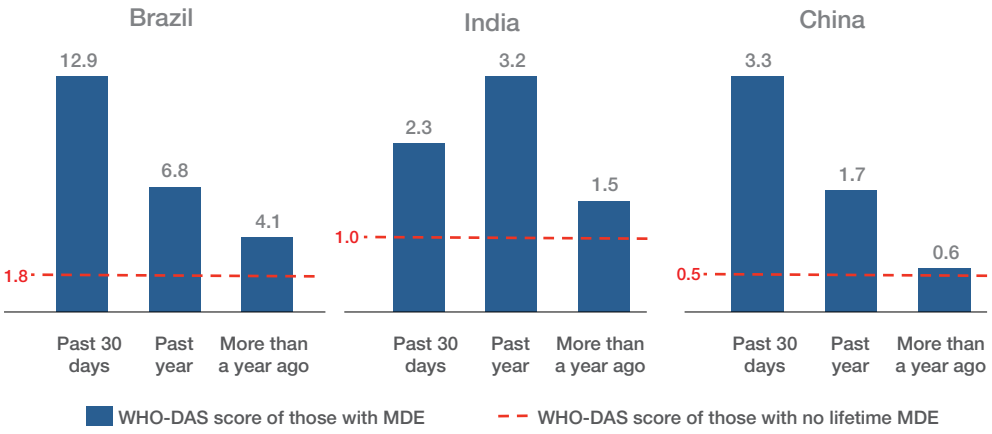
128 Bitran et al (2010), 'After Chile's health reform: increase in coverage and access, decline in hospitalization and death rates', Health Affairs 29(12): 2161-2170.

129 Araya et al (2003), "Treating depression in primary care in low-income women in Santiago, Chile: a randomised controlled trial", Lancet, 361, 995-1000.

130 WHO (2010), 'Mental health and development: targeting people with mental health conditions as a vulnerable group'.

131 McDaid et al (2008), 'Barriers in the mind: promoting an economic case for mental health in low – and middle-income countries', World Psychiatry 7: 79-86.

Figure 22: Functional impairment (WHO-DAS scores) of major depressive episodes (MDE) by time from last MDE



Source: Bromet et al (2011), 'Cross-national epidemiology of DSM-IV major depressive episode', BMC Medicine 9:90 Note: WHO-DAS – WHO Disability Assessment Schedule

- A survey conducted in Brazil examined work productivity among the non-depressed, the treated-depressed population (n=184), and the untreated depressed population (n=155). The survey found that those treated for depression had higher mean productivity loss than those who were untreated in all productivity measures (absenteeism, overall impairment and activity impairment) except for presenteeism, although the statistical significance of the difference was not examined. The study did not specify which medicines were being used among those treated for depression. Additionally, the treated group had higher proportion of self-reported moderate (58.5% vs. 51.9%) and severe (31.5% vs. 22.3%) depression compared to the untreated group, which likely influenced the productivity levels in each group.[132] As the study did not control for differences between the treated and untreated depressed group, the differences between these two groups do not necessarily reflect the value of treatment.

Given the limited evidence from MICs on the wider societal benefits of antidepressants, it is useful to briefly examine the evidence for HICs as a benchmark of the possible societal gains if depression is treated. A study conducted in Canada found that patients who used antidepressants according to guidelines (recommended first-line agents at recommended doses) were more likely to return to work than to claim long-term disability benefits or leave their employment, compared to those who did not use antidepressants according to guidelines. Those who used antidepressants early in their disease were likely to have a shortened disability episode.[133] A study in the US found that by training primary care doctors to provide high-quality psychosocial and pharmacological care, depressed patients were 6.1% more productive than patients treated by a 'normal' primary care doctor and had 22.8% less absenteeism.[134] Thus there is evidence from HICs that use of antidepressants according to guidelines, supervised by adequately trained physicians, can result in wider benefits to society.

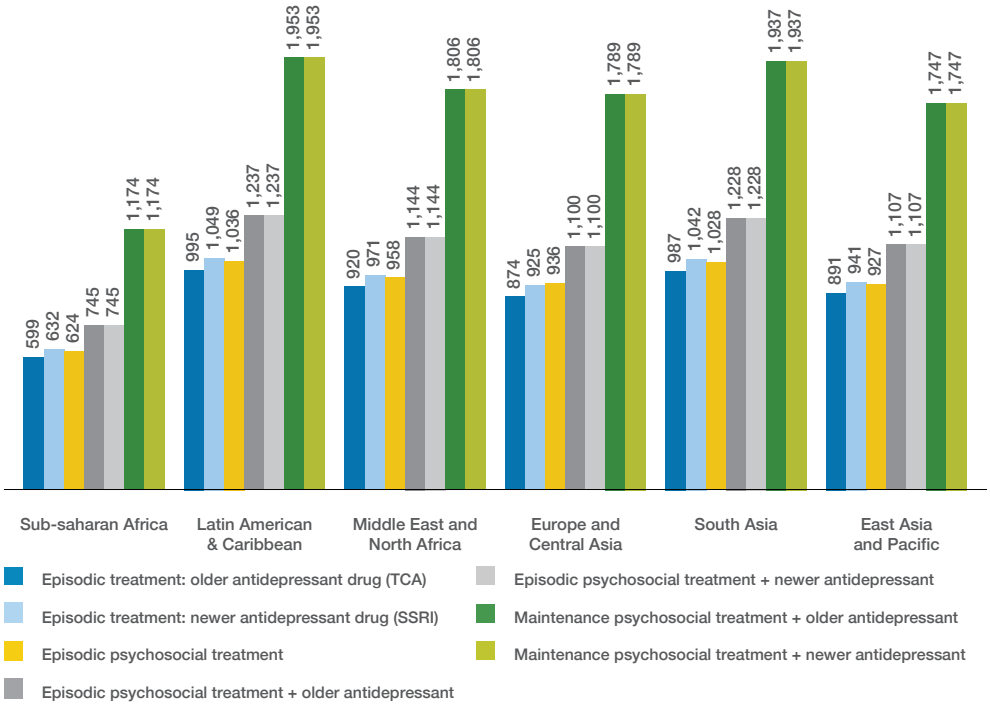
132 Fujii et al (2012), 'Prevalence, awareness, treatment, and burden of major depressive disorder: estimates from the National Health and Wellness Survey in Brazil', Value in Health Regional Issues 1: 235-243.

133 Dewa et al (2003), 'Pattern of antidepressant use and duration of depression-related absence from work', British J Psy 183: 507-513.

134 Rost et al (2004), 'The effect of improving primary care depression management on employee absenteeism and productivity: a randomized trial', Med Care 42(12): 1202-1210.

While there are no backward-looking studies on the benefits of antidepressants in MICs, studies have been conducted that projected the potential societal benefits if antidepressants were used. A global WHO-CHOICE study, which included both HICs and MICs, found that if 50% of depressed patients received episodic treatment with antidepressants and/or psychotherapy, 600-1200 DALYs would be gained annually per one million population. The gains would be even higher (1200-1900 DALYs averted) if depression was proactively treated and treatment was maintained, as recurrent episodes could be prevented.[135] As Figure 23 shows, the DALYs averted are higher if SSRIs are used for episodic treatment compared to TCAs, but this slight gain is evened out if patients receive episodic or maintenance psychosocial treatment.

Figure 23: DALYs averted per year (per million population) if 50% of depression sufferers receive treatment



Source: Chisholm on behalf of WHO-CHOICE (2005), 'Choosing cost-effective interventions in psychiatry: results from the CHOICE programme of the World Health Organization', World Psychiatry 4:1

3.4. THE VALUE OF MEDICINES FOR DEPRESSION IN MICS

Depression is a common mental disorder that has significant consequences for the patient's quality of life and at its worst, depression can lead to suicide. It has a high burden of disease within the MICs in terms of health years lost. Although mortality due to depression is relatively low, accounting for less than 0.05% of deaths due to NCDs, the number of DALYs lost was as high as 48.5 billion DALYs across the MICs, accounting for 9% of DALYs lost due to NCDs.

There are several classes of antidepressants with different mechanisms of action. All antidepressants are similarly effective in treating moderate to severe depression, but

135 Chisholm on behalf of WHO-CHOICE (2005), 'Choosing cost-effective interventions in psychiatry: results from the CHOICE programme of the World Health Organization', World Psychiatry 4:1.

they differ in terms of adverse effects.[136] Selective serotonin reuptake inhibitors (SSRIs) were launched in the mid to late 1980s, although some were launched in the last few years. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a newer class of antidepressants that developed after 1990, and there are fewer molecules in this class.

Regarding access, very few MICs have national strategies targeted specifically at depression. Most of the MICs studied – Brazil, Russia, India, and China – only have national mental health policies, although they are geared more towards psychotic conditions than depression. Only Chile has a program specifically aimed at depression, which was expanded nationally in 2003. Even so, all the selected countries have at least a molecule from two antidepressant classes on their EDL, meaning that in theory they should be widely available to the population. Additionally all of the selected countries except for Russia have guidelines regarding the use of antidepressants among depression sufferers. However, despite the availability of medicines, evidence suggests that depression is rarely treated in MICs. There are estimates that of the selected countries, only around 10% of people with depression see a healthcare professional or receive medication for the condition. The exception is Chile, where 20% of depression sufferers received treatment and, after the inclusion of depression as a priority health issue, the percentage treated increased to 34% in 2008.

In terms of value, treatment for depression has brought clinical and therapeutic benefits within the selected countries. For example, there is a large amount of evidence suggesting that the primary care program in Chile is effective when used, although even in Chile there is a problem associated to awareness and even in this case it is difficult to attribute value to medicines specifically.

There is limited evidence regarding the link between the use of antidepressants and non-clinical benefits. Very few papers examined the effect on cost savings and socioeconomic elements. However, there were papers that found less functional impairment and fewer lost workdays among people with lower levels of depression. This suggests that if a greater number of depression sufferers in MICs receive treatment for depression, the clinical benefits could translate into wider gains for society. There is evidence in HICs that antidepressants result in lower productivity loss, suggesting that if depression were more frequently diagnosed and treated in MICs, antidepressants could bring greater value, a hypothesis that is supported by a WHO DALYs saved projection study. Table 11 summarises the main findings of the depression study.

136 WHO (2009), 'Pharmacological treatment of mental disorders in primary health care'.

Table 11: Summary of the findings related to treatment, usage and value of medicines for depression within BRIC + Chile

	BRAZIL	RUSSIA	INDIA	CHINA	CHILE
National strategy against depression	Mental health policy, 1991	Mental health strategies	National Mental Health Programme (NMHP), 1982	Mental health plans	National Depression Program (PNDTD) 2003
Inclusion in EDL	TCA, MAOI, SSRI, other	TCA, SSRI	TCA, SSRI	TCA, MAOI, SSRI, SNRI, other	TCA, SSRI, SNRI, other
Treatment received*	17%	3%	8%	9%	27%
Existence of treatment guidelines	Yes	No	Yes	Yes	Yes
Evidence on the value of treatment	Clinical	Clinical	Clinical	Clinical	Clinical; Cost control

Source: CRA analysis; *Treatment rates for any kind of treatment received for depression, pharmacological and non-pharmacological; Analysis using country-specific sources[137]

An interesting aspect of depression that may present one of the most significant barriers is the disbelief in the efficacy of treatment or the stigma attached to having a mental illness. A study of those aged 60 to 93 years old in Russia found that 61% of respondents thought that depression was a sign of weakness, compared to 6% of respondents in the US.[138] This may help to explain that only 8% of depression sufferers receive treatment in LICs and MICs, compared to 29% in HICs.[139]

In addition to the stigma of depression, there are also barriers to diagnosis of depression in MICs due to lack of awareness of the disease and insufficient training in diagnosing and treating it. As a result, depression sufferers are often not treated in MICs, even though antidepressants are usually available on the EDL. Cost can be a reason for lack of treatment, while in other cases it may be due to lack of access to physicians or, as mentioned earlier, fear of stigmatisation.[140] Access to antidepressants may increase in MICs if they overcome treatment barriers and adopt programs similar to those used in HICs, which lowered barriers to depression treatment. A national depression initiative in Australia, 'beyondblue', was able to change attitudes regarding the mental illness. The program led to a change in beliefs about the benefits of seeking help for depression, as well as counselling and medication treatment for the illness.[141] Another example is Japan, which provided training in screening for depression through a community-based public health suicide prevention programme. The program was able to lower suicide rates in participating prefectures.[142] Emulating such HIC awareness programs may remove barriers to depression treatment in MICs.

137 Brazil and Russia: Simon et al (2004), 'Prevalence and predictors of depression treatment in an international primary care study', Am J Psychiatry 161:9; India: average of low and middle income countries, Academy of Medical Sciences (2008), 'Challenges and priorities for global mental health research in low- and middle-income countries'; China: Zhang (2010), 'Major depressive disorder treatment guidelines in China', J Clin Psychiatry 71: e06; Chile: Bitran et al (2010), 'After Chile's health reform: increase in coverage and access, decline in hospitalization and death rates', Health Affairs 29(12).

138 Turvey et al (2012), 'Cultural differences in depression-related stigma in late-life: a comparison between the USA, Russia, and South Korea', International Psychogeriatrics

139 Academy of Medical Sciences (2008), 'Challenges and priorities for global mental health research in low – and middle-income countries'.

140 Marcus et al (2012), 'Depression: a global public health concern', World Federation for Mental Health.

141 Jorm et al (2005), 'The impact of beyondblue: the national depression initiative on the Australian public's recognition of depression and beliefs about treatments', Aus NZ J Psychiatry 39(4): 248-254.

142 Nam et al (2008), 'Creating public awareness in Asia of depression as treatable and suicide as preventable' in WHO, 'Suicide and suicide prevention in Asia'.

4

DIABETES

Diabetes has become one of the most common NCDs in the world, representing one of the most challenging public health problems of the 21st century. There are two main types of diabetes:

- **Type 1 diabetes (T1D)** results from the autoimmune destruction of the pancreatic beta cells, the producers of insulin. T1D can occur at any age, although most cases develop amongst children, teenagers and young adults. There is currently no means of preventing or curing T1D.

- **Type 2 diabetes (T2D)** is characterised by insulin resistance, impaired insulin secretion, or both. It is the most common form of diabetes. This type of diabetes is typically diagnosed after the age of 40, though recently T2D has also been diagnosed in younger adults, and occasionally among adolescents. T2D has a strong genetic (familial) predisposition, which is exacerbated by lifestyle factors including obesity and lack of exercise. Thus it is potentially preventable in a substantial proportion of the population. Most people diagnosed with T2D will eventually require medication, which may include insulin therapy.

Diabetes receives a lot of attention from HICs, mostly due to the high number and costliness of its co-morbidities.[143] As an example, the risk for CHD increases fivefold for diabetics, and about 65% of diabetics die from heart disease and stroke.[144] In addition to cardiovascular complications, there is an increased risk of eye and kidney diseases and limb amputations Given this, it is not surprising that developed countries—where people tend to have more-sedentary lifestyles and a greater risk of diabetes—have invested in addressing the disease.

In this chapter we focus on T2D. We provide a brief overview of treatment options for T2D within HICs and MICs. Using the large amount of evidence on the benefits of diabetes drugs in HICs, such an approach allows us to see if the benefits in HICs (as illustrated by evidence from Australia, Canada, the United Kingdom and the US) as a base, we have examined if the same evidence exists for MICs (as illustrated in China).

4.1. EVOLUTION OF TREATMENT OPTIONS FOR DIABETES

Treatment is dependent on the type of diabetes the patient has. The main categories of treatment include insulin therapy and oral medication.

- **T1D** patients are treated with insulin therapy (also known as insulin replacement therapy).[145]

- **T2D** patients are recommended oral hypoglycaemic agents ('oral anti-diabetic drugs') and insulin, in addition to lifestyle changes (e.g. regular exercise, dietary improvements, tobacco cessation).[146]

143 See, for example, IDF, 'What is diabetes?', http://www.idf.org/node/23928

144 Diabetes.UK, 'Cardiovascular disease', http://www.diabetes.org.uk/Guide-to-diabetes/Complications/Cardiovascular_disease/; National Diabetes Education Program, http://ndep.nih.gov/media/CVD_FactSheet.pdf

145 WHO (2013), 'Diabetes', WHO fact sheet, 312.

146 NHS, 'Causes of type 2 diabetes', NHS online information guide.

THERAPY OPTIONS FOR THE TREATMENT OF T2D

Oral anti-diabetic drugs (OADs)

Medication for diabetes has been available since the 1920s, and the anti-diabetic effect of sulphonylurea was discovered in the early 1940s.[147,148] These older treatments have either been discontinued due to poor safety profiles or replaced by newer, more efficacious products.[149]

As seen in Figure 24, there was a phase of innovation starting in the early 1990s with the introduction of three new classes (alpha-glucosidase inhibitors, meglitinides and thiazolidinediones). Another round of innovation occurred from the mid-2000s with an additional three new classes (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors).[150]

- **Sulphonylurea** is an insulin secretagogue[151] that increases the efficacy and production rate of insulin by the pancreas.[152] Almost all first-generation sulphonylureas have been discontinued. Examples of second-generation sulphonylureas include glipizide (Glucotrol) and glimepiride (Amaryl).

- **Biguanides** is the class name for metformin and contains no other products. Metformin has been the universal first line therapy for T2D.[153]

- **Alpha-glucosidase inhibitors (AGI)** slow down the digestion of starch in the intestinal tract, which subsequently reduces sugar levels after meals. Examples include miglitol and acarbose.

- **Meglitinide**, also known as glinides, similarly to sulphonylureas, are secretagogues. Examples include repaglinide and nateglinide.

- **Thiazolidinediones**, like biguanides, are insulin sensitisers. Examples include pioglitazone and rosiglitazone.

- **Glucagon-like peptide-1 (GLP-1)** agonist engages a specific G-protein receptor. Continuous activation of this receptor (GLP-1 receptor) also increases insulin synthesis.[154] Examples of GLP-1 agonists include exenatide and liraglutide.

- **Dipeptidyl-peptidase-4 (DPP-4)** inhibitors, inhibit degradation of hormones that are involved in increasing insulin release.[155] Examples include saxagliptin and alogliptin.

147 Diabetes UK (2010), 'First use of insulin in treatment of diabetes 88 years ago this week', Diabetes UK article.

148 Henquin (1992), 'The fiftieth anniversary of hypoglycaemic sulphonamides. How did the mother compound work?' Diabetologia, vol. 35, 907-912.

149 All classes include input from Diabetes UK, 'Diabetes Drugs'.

150 All classes include input from Diabetes UK, 'Diabetes Drugs'.

151 Term given to a substance that causes the secretion of another substance.

152 Gromada (1995), 'Effects of the hypoglycaemic drugs repaglinide and glibenclamide on ATP-sensitive potassium channels and cytosolic calcium levels in beta TC3 cells and rat pancreatic beta cells' Diabetologia, Vol.38, 1025-1032.

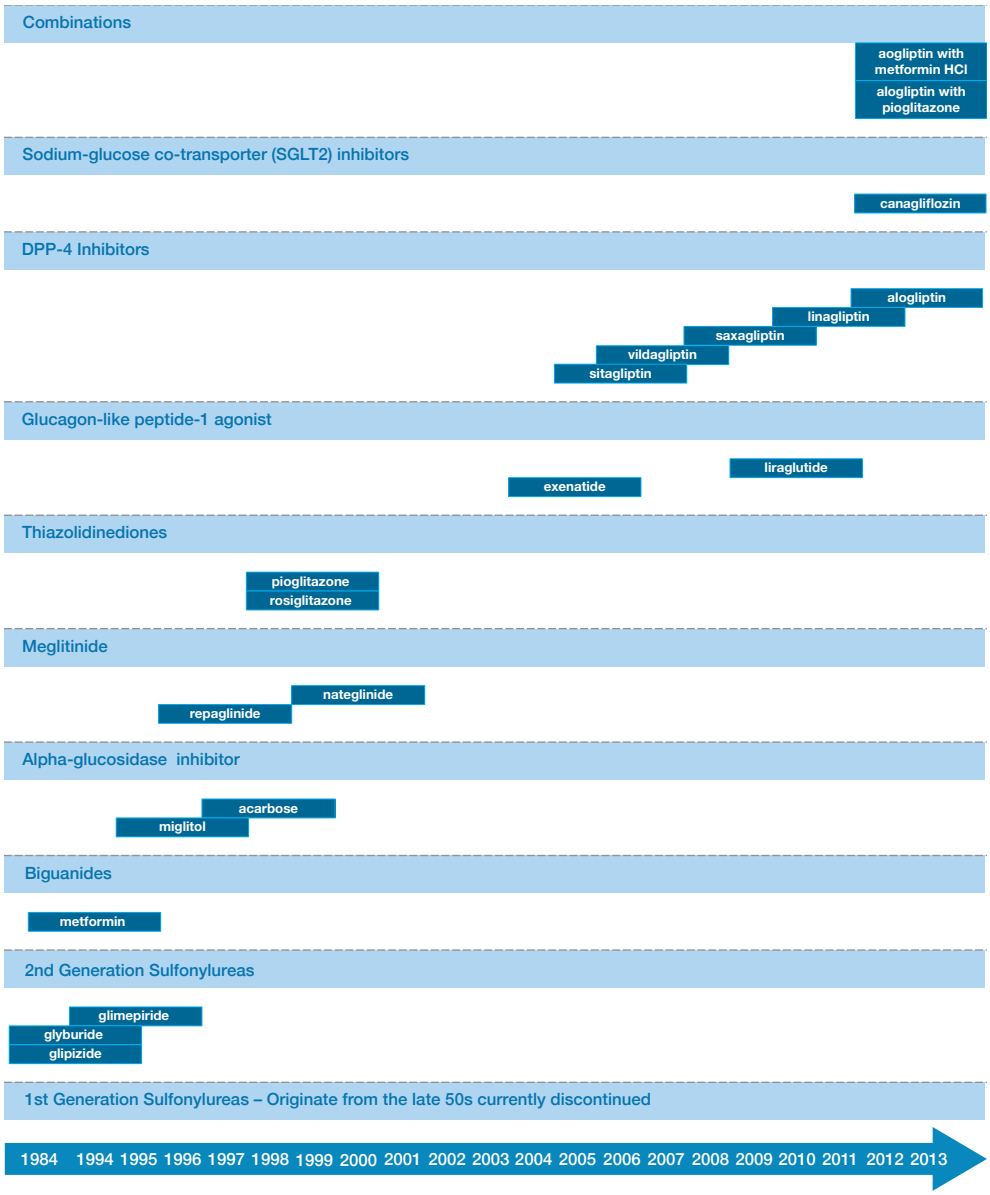
153 Halimi (2008), 'Combination treatment in the management of type 2 diabetes : focus on voldagliptin and metformin as a single tablet', Vascular Health and Risk Management, vol. 4, iss. 3, 481-492.

154 Doyle and Egan (2007), 'Mechanisms of Action of GLP-1 in the Pancreas' Pharmacology & Therapeutics, vol. 113, iss. 3, 546-593.

155 Thornberry and Gallwitz (2007), 'Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4)', PubMed, vol. 23, iss. 4, 4790486.

- **Sodium-glucose co-transporter (SGLT2)** inhibitors are a class of glucose-lowering drugs which provide fully insulin-independent mechanism of action to managing the glycemic levels of a patient (by blocking glucose reabsorption in the kidney).[156] Examples include canagliflozin and dapagliflozin.

Figure 24: First appearance of novel treatment classes of OAD



Source: CRA analysis

Insulin

Hypoglycaemic agents all try to influence the body's secretion of insulin. Insulin however, is itself also used to treat T2D patients and is typically used after poor control on OADs. Insulin is classified according to the length of action, which determines whether it is used as basal or bolus insulin. Basal insulin is used to keep blood glucose

156 Valentine (2012), 'The role of the kidney and sodium-glucose cotransporter-2 inhibition in diabetes management', Clinical Diabetes, vol.30, iss. 4, 151.

at consistent levels when fasting, while bolus insulin is taken at meal times to control blood glucose after meals.[157] Molecular makeup (animal, human and analogue) also differentiates the insulins. At present, human and analogue insulins are the most commonly used.[158] Insulin therapy is classified into several different types:[159]

- **Rapid-acting (analogue) insulin**: injected either just before, with, or after food, with a peak at between 0 and 3 hours. Generally lasts between 2 and 5 hours. Examples are aspart and lispro.

- **Short-acting (human) insulin:** injected 15 to 30 minutes before meals to compensate for the rise in blood glucose levels caused by eating. This type has a peak action of 2 to 6 hours and last up to 8 hours. Examples are regular insulin Novolin R and Humulin R.

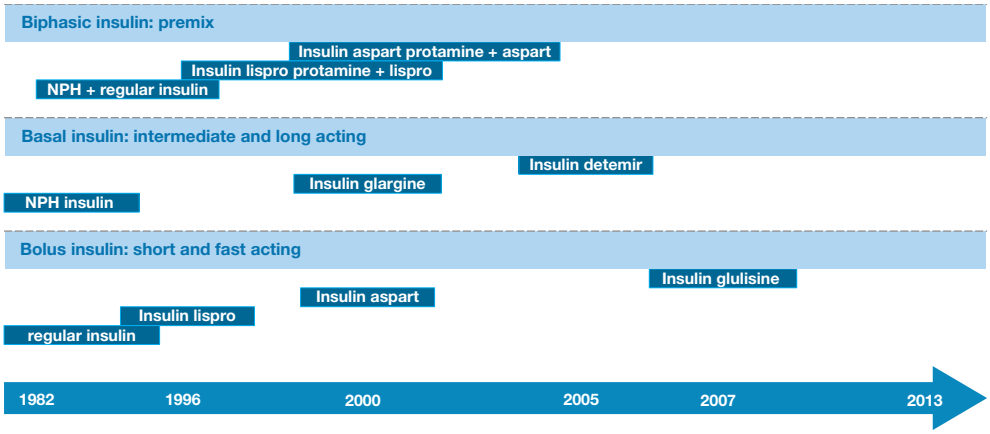
- **Intermediate-acting (human) insulin:** taken once or twice a day in combination with short – or fast-acting insulins to provide a background insulin level. Their peak is between 4 and 12 hours and can last up to 30 hours. NPH insulin is an example.

- **Long-acting (analogue) insulin:** as with intermediate-acting insulin, injected to provide background insulin in combination with short – or fast-acting insulin. Does not have a peak action and does not need to be taken with food. Examples are glargine and detemir.

- **Premix insulin:** a biphasic insulin that provides basal and bolus coverage without having to be injected separately. The basal coverage can be in the form of intermediate – or long-acting insulins, while bolus coverage can be in the form of short – or rapid-acting insulin.

Although the first commercialisation of animal derived insulin began in the 1920s, we focus on synthetic "human" insulin. Figure 25 demonstrates the evolution of FDA-approved insulin therapies.

Figure 25: First appearance of novel treatment classes of synthetic human insulin



Source: CRA analysis. Note: insulin degludec, a long-acting insulin, was approved by the EMA in 2012 but not the FDA

157 Diabetes UK, 'Basal bolus – basal bolus injection regimen', http://www.diabetes.co.uk/insulin/basal-bolus.html

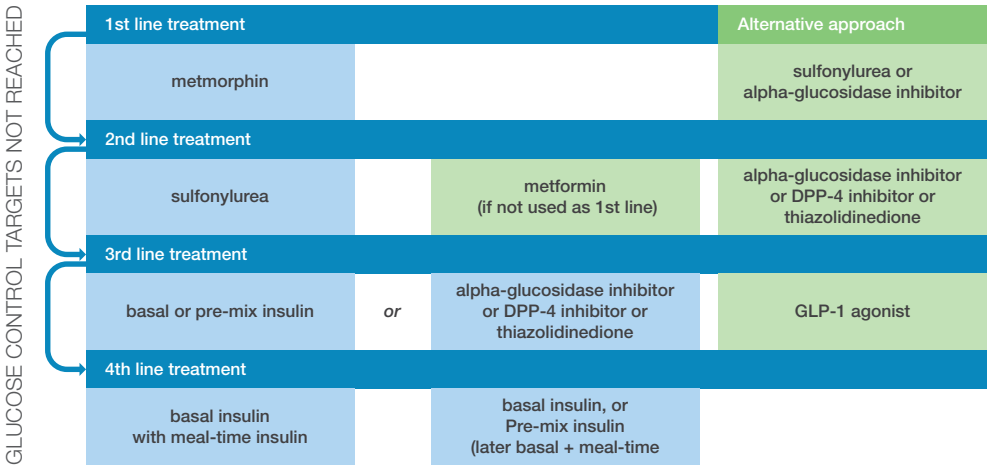
158 Diabetes UK, 'The three groups of insulin', Diabetes UK guide to diabetes: https://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Insulin/

159 Diabetes UK, 'The main types of insulin', Diabetes UK guide to diabetes: https://www.diabetes.org.uk/Guide-to-diabetes/Treatments/Insulin/

RECOMMENDED FIRST-LINE TREATMENT FOR DIABETES IN IDF GUIDELINES

The International Diabetes Federation introduced its first 'Global Guideline for Type 2 Diabetes'' in 2005. The guidelines were developed based on clinical elements, cost-effectiveness, and resources of less-wealthy countries. The guidelines were last reviewed in 2012.[160] Figure 26 shows how different medicines should be used in sequences if glucose control targets are not reached.

Figure 26: IDF diabetes guidelines, 2012



Source: International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force.
Note: Limited care principles are the same as recommended care; however, attention must be given to cost and generic alternatives (e.g. human insulins can provide most of the gains that are achieved with analogue insulins). Comprehensive care also follows the same principles, but more expensive therapies and insulins may be considered

4.2. ACCESS TO MEDICINES FOR DIABETES

The first issue to examine is the relative access in our HIC and MIC countries to the innovative medicines described above.

All major diabetes treatments are available in the selected HICs, with some differences in uptake for the latest anti-diabetic agents.

To determine the degree of access in China, we have followed the approach of the other case studies, first examining the introduction of diabetes medication in the Chinese essential drug list (EDL), the existing evidence on access to treatments for diabetes in China, the use of clinical guidelines on the treatment of diabetes and the existence of a national strategy to fight against diabetes.

The introduction of diabetes medication in the Chinese EDL

Insulin and OADs were included in the Chinese EDL in 2002 (see Table 12). China's 2002 EDL includes OADs from the meglitinide and thiazolidinediones class, which

160 International Diabetes Federation (2012) 'Global Guideline for Type 2 Diabetes', IDF, 2012 Clinical Guidelines Task Force.

have been removed from the 2012 edition of the EDL.[161] The bulk of OADs fall within the second-generation sulphonylureas class. This is the oldest of the classes, and even with new classes available, the majority of hypoglycaemic medicines on China's 2012 EDL are within this category.[162] The 2002 EDL does not provide further detail on the type of insulin, but the 2012 EDL specifies that insulins encompass short-acting, intermediate-acting, and premix animal and human insulins. Analogue insulins were not included in the 2012 EDL.

Table 12: Year of introduction of treatment classes used for the treatment of diabetes in China

	YEAR OF INTRODUCTION
Sulphonylureas	2002
Biguanides	2002
AGI	2002
Meglitinide	2002*
Thiazolidinediones	2002*
GLP-1 agonist	-
DPP-4 inhibitor	-
Sodium-glucose co-transporter inhibitor	-
Insulin	2002

Source: CRA analysis using Chinese 2002 and 2012 Essential Drugs List. Note: *Indicates that the a molecule in the class was introduced in that year, but is not included in the 2012 EDL

The existing evidence on access to treatments for diabetes in China

A study by IMS Health (IMS) estimates the anti-diabetic medication usage in China in 2008.[163] The study uses WHO's 'defined daily dose' (DDD) to calculate the number of patients receiving treatment based on the total anti-diabetic drugs use in the hospital setting.

Sulphonylureas are the most commonly used medicine class in China with over one million patients receiving this treatment. This is followed by biguanides with only 341,376 users (Figure 27). Another study found that biguanides (i.e. metformin) are the most prescribed first-line OADs in China, followed by first-generation drugs from the AGI and meglitinide classes, which had a 37.6% penetration rate (compared to 1.3% in the US). The newer classes, namely DPP-4 inhibitors and GLP-1 agonists, has limited uptake in China (2.7% of the patient population, compared to 42% in the US). This corroborates three of the data points in Figure 27[164] and supports the hypothesis that drugs included in EDLs are commonly used within the population.

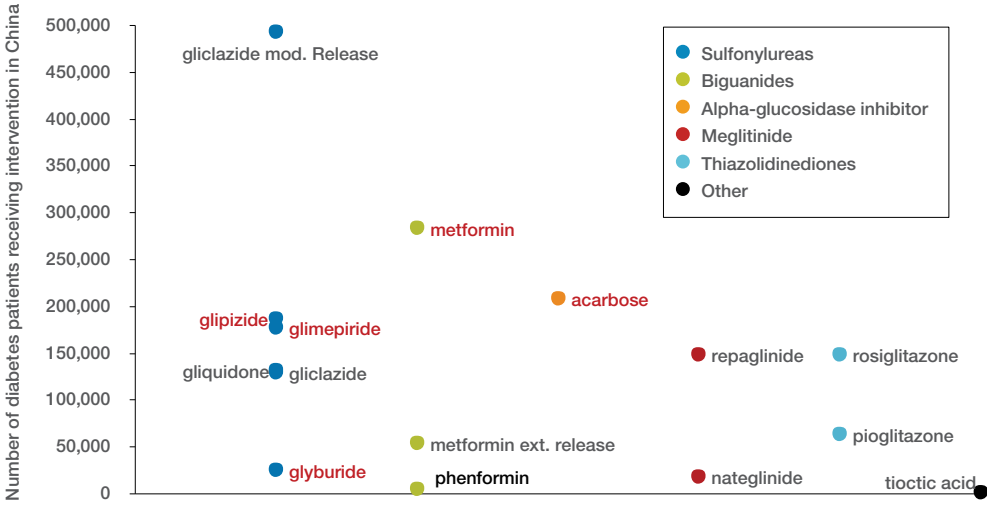
161 Chinese National Essential Drug List, 2002. Available at http://www.sda.gov.cn/gyja438/x07.htm, http://www.sda.gov.cn/gyja438/x04.htm, and http://www.sda.gov.cn/gyja438/x11.htm

162 Chinese National Essential Drug List, 2012. Available at http://itrade.gov.il/china-en/2013/04/23/national-essential-medicine-list-2012-edition-released/

163 Hospitals are the primary drug dispensers in China as pharmacies mainly sell OTC drugs and traditional Chinese medicines.

164 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

Figure 27: Estimated number of patients receiving OADs in China by molecule, 2008



Source: CRA analysis using IMS, (2009), 'Examining diabetes and anti-diabetic medication use in low – and middle – income countries using the IMS core diabetes model', Core Center for Outcomes Research. Note: Medicines are grouped by class on the x-axis; medicines in red represent those on the Chinese Essential Drug List (2012 version)

As seen in Figure 28, human and animal insulins are the most popular types of insulins used in China. The use of the newer analogue insulin class is still very limited by comparison. Interestingly, insulin use is higher in China compared to the US (35.9% vs. 20%), which the study attributes to poor blood sugar control of T2D patients in China.[165]

Figure 28: Estimated number of patients receiving insulins in China, 2008

Source: CRA analysis using IMS, (2009), 'Examining diabetes and anti-diabetic medication use in low – and middle – income countries using the IMS core diabetes model', Core Center for Outcomes Research. Note: Insulins are grouped by class on the x-axis; medicines in red represent those on the Chinese Essential Drug List (2012 version)

If we assume that a diabetic patient will be on only one therapy over the period of a year (i.e., one type of OAD or one type of insulin) and compare this with the 2007 IDF diabetes prevalence estimates for China, then there were at most 6.5% of diabetes

165 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

patients receiving some sort of diabetes therapy (although this is an overestimation for a number of reasons).[166] In other words, even with these generous assumptions, 93.5% of diabetics did not receive therapy in 2008 in China.

The use of clinical guidelines on the treatment of diabetes

The Chinese Diabetic Society (CDS) is the leading national diabetes organisation in China. The CDS's mission is to prevent and treat diabetes through education, research, and the instilling of good medical practice.[167]

The CDS developed the first Chinese diabetes treatment guidelines in 2000 based on the 1997 American Diabetes Association (ADA) guidelines and WHO 1999 guidelines. The CDS guidelines were updated in 2004, 2008 and 2009. They provide guidance on aspects of diabetes treatment such as diagnosis, classification, treatment goals and diabetes management.[168]

Chinese national strategy to fight against diabetes

Since 2004, the CDS has launched a project nationwide promoting the 'Chinese Guidelines of Diabetes Prevention and Treatment' (Guideline Promotions) which is one of two branches of the China National Diabetes Management Program (CNDMP). The objective of the CNDMP is to establish an effective model for the prevention, detection and treatment of diabetes across different regions in China.[169] As part of the 'Guideline Promotions', China started a five-year programme to train 8,600 doctors (3,600 doctors in 36 major cities and 5,000 in smaller cities). A total of 5,550 doctors were trained through the project (3,050 short of the original aim).[170]

In addition to the CNDMP, the Chinese Ministry of Health and the Development and Reform Commission signed the 'China National Plan for Non-Communicable Diseases Prevention and Treatment (2012-2015)'. As a result, the MoH is in the process of writing a specific action plan for diabetes along with other diseases such as COPD, cancer, and CVD.[171]

A COMPARISON OF ACCESS TO DIABETES TREATMENT IN HICS AND CHINA

Unsurprisingly, we find that diabetes therapies, both old and new classes, were widely available within the HICs. In China, the evidence available shows that the coverage rates are relatively lower than in HICs, mainly because awareness of the disease is still

166 First, we used 2007 data, as 2008 data is not available. Given the positive trend experienced in China, we believe that in 2008 the population would have been bigger. Second, by using the whole diabetes population, we assume that all patients are at the same stage of the disease. Finally, patients will not necessarily be on only one therapy. For example, it is common for T2D patients to be on an OAD and insulin therapy, while those in the later stages of the disease may be on two types of insulin therapy.

167 Chinese Diabetes Society website: http://www.cdschina.org/english/page.jsp?id=33.

168 Wang (2011),'Diabetes Care in China Impacts of Traditional Chinese Medicine (TCM) and Insurance on Quality and Utilization', Pardee Rand Graduate School dissertation.

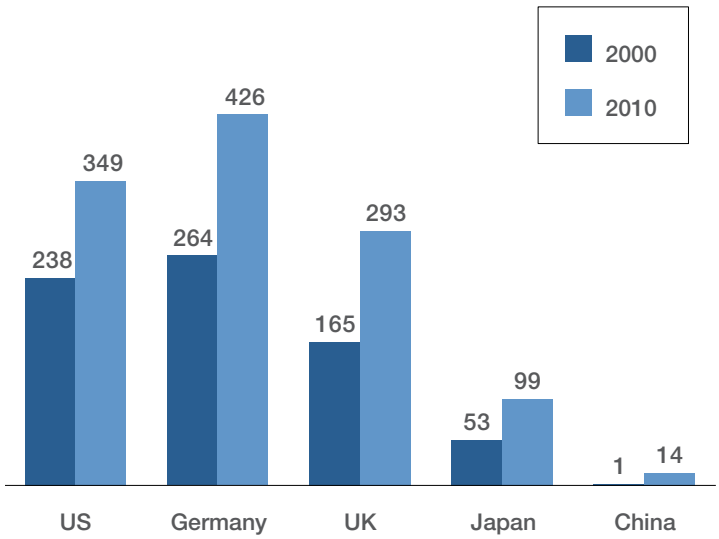
169 Chinese Diabetes Society, (2010), 'The Promotion of the Chinese Guideline of Diabetes Prevention and Treatment in China', Chinese Diabetes Society.

170 Chinese Diabetes Society, (2010), 'The Promotion of the Chinese Guideline of Diabetes Prevention and Treatment in China', Chinese Diabetes Society.

171 WHO (2013), 'Cardiovascular diseases', WHO Representative Office China, http://www.wpro.who.int/china/mediacentre/factsheets/cvd/en/index.html, accessed May 15, 2013.

low and most of the sufferers fail to be diagnosed. Additionally, although insulin and oral hypoglycaemic drugs are included in the Chinese EDL, they tend to be from the older classes. For example, drugs from the AGI and meglitinide classes had a 37.6% penetration rate, while the newer DPP-4 inhibitors and GLP-1 agonists had only 2.7% penetration. By contrast, in the US the former has only 1.3%, while the newer OADs have 42% penetration.[172] Use of insulins in China has increased dramatically in the last 10 years due to increased prevalence of or access to insulin, but it is still low compared to HICs (see Figure 29).

Figure 29: Insulin consumption in selected countries – average insulin units per inhabitant



Source: Novo Nordisk (2011), 'The global diabetes care market'

The Chinese government has recently launched the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, which aims to develop a plan for NCD. There is the possibility that this plan will increase access to diabetes treatment in China.

4.3. THE VALUE OF TREATMENT FOR DIABETES

In this section we first provide an overview of the benefits that diabetes treatments have brought to HICs, focusing on recent literature published in HICs, and we then see if the same effects have been found in China.

THE BENEFITS OF DIABETES DRUGS ACHIEVED WITHIN HICS[173]

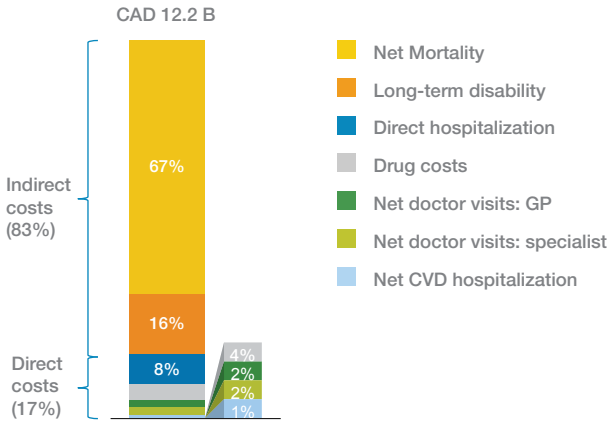
The economic burden of diabetes has been estimated in a number of HICs. These show that the economic burden is largely represented by indirect costs. For example, the

172 IPSOS (2013), 'Majority of type 2 diabetes patients in China yet to benefit from latest generations of oral treatment'.

173 We have chosen in this case study to use Australia, Canada and the UK as the HIC comparators. There is extensive data available in Europe from "Diabetes expenditure, burden of disease and management in 5 EU countries" . This is available at http://www.lse.ac.uk/LSEHealthAndSocial-Care/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf

indirect cost of diabetes in Canada represented 83% of total costs. The total cost of diabetes was CA$12.2 billion, of which direct costs (i.e., medical costs) amounted to CA$2 billion in 2007 (Figure 30).

Figure 30: Economic burden of diabetes in Canada, in CAD, 2007



Source: Canadian Diabetes Association (2009), 'An economic tsunami the cost of diabetes in Canada'. Note: CAD – Canadian dollars

Therapeutic/Clinical benefits

The link between the use of diabetes drugs and the reduction of mortality rates in developed economies has been extensively studied. Prevention T2D has been shown to bring therapeutic benefits as it reduces the complications and other risks associated with the disease. Indeed, a recent report developed by Diabetes Australia reviewed the most relevant publications on the clinical benefits of treating diabetes, for example, they found:[174,175]

- A UK study found that effective treatment of T2D reduced the probability of complications such as heart attack (by more than 50%), stroke (by 44%) and serious deterioration of vision (by up to 33%). The study's definition of 'effective treatment' included close monitoring and control of blood glucose levels, blood pressure and lipids.[176,177] This would be achieved through several forms, including diabetes therapy.

- A 10-year study in Denmark demonstrated that by intervening simultaneously on multiple factors when treating T2D (glucose, blood pressure, cholesterol, etc.), the risks of developing severe complications were reduced by about 50% over 13 years.[178]

174 Shaw, et al (2012), 'Diabetes: the silent pandemic and its impact on Australia', Baker IDI, Diabetes Australia and Juvenile Diabetes Research Foundation. It is worth noting that most of the sources cited by Diabetes Australia were also used by the Canadian Diabetes Association

175 Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

176 The diabetes control and complications trial research group (1993), 'The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus', New England Journal of Medicine, 329; Nathan et al (2005), 'Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes', New England Journal of Medicine, 353; UKPDS group (1998), 'Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes IKPDS33', The Lancet, 352.

177 The UKPDS was the largest clinical research study in diabetes conducted at the time and it is still a reference that is used within most of the diabetes associations.

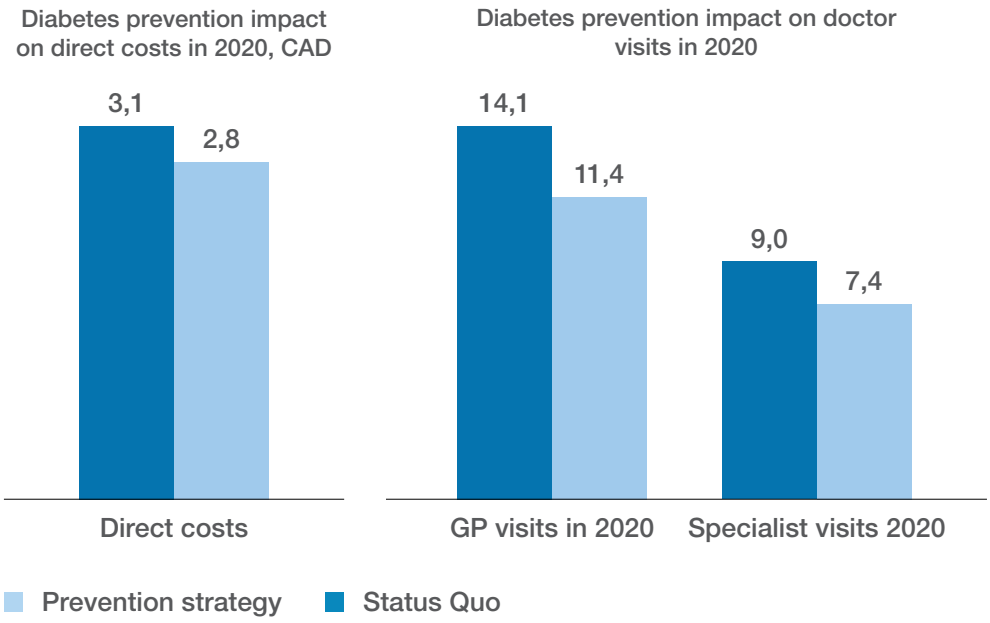
178 Gaede, et al (2008), 'Effect of a multifactorial intervention on mortality in Type 2 diabetes', New England Journal of Medicine, 359.

- Diabetes-related complications are a major driver of service use and can multiply costs per patient. For example, about 34% of the total hospital in-patient days for diabetes patients are due to cardiovascular disease.[179] Similarly, end-stage renal disease has been shown to increase costs by as much as 771%.[180]

Controlling costs in the healthcare system

There are many studies that have estimated the cost associated with untreated diabetes.[181] There have been a number of estimates of the cost savings that achieved if both preventive and appropriate management of diabetes were implemented. In Canada, the direct and indirect costs were estimated if the diabetes incidence rates fell by 2% yearly. In such a situation direct costs would decrease by 9% by 2020, with the greatest decline from reduced GP and specialist visits due to improved diabetes education and management (see Figure 31). The authors did not project the effect of reduced complications on costs of hospitalisation, amputation (which is estimated by the IDF as more than 25 times greater in patients with diabetes), or medication use.[182]

Figure 31: Diabetes prevention program impact on direct costs and doctor visits in Canada, 2020



Source: Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'

Wider benefits to society

In terms of wider benefits we have not found evidence related directly to T2D. However, a study in England estimated the cost savings related to T1D if patients had their blood

179 "Economic Costs of Diabetes in the US in 2007". American Diabetes Association. Diabetes Care 2008; 31:596-615.

180 Jonsson B. "Revealing the Cost of Type II Diabetes in Europe". Diabetologia 2002; 45:S5-S12

181 For example, costs estimates for gangrene treatment, ulcer treatment and lower limb amputation were provided in Bakker K et al. "Practical Guidelines on the Management and Prevention of the Diabetic Foot". Diabetes Metab Res Rev 2012; 28(Suppl 1):225–231.

182 Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

sugars tightly controlled.[183] The authors estimated that if T1D patients were administered intensive glucose control, an average of 10 deaths per year could be avoided in the first five years with an average annual value for the English economy of £10 million. This represents an annual average of 400 years of life lost (YLL) and a total of 1,400 avoidable DALYs lost, costing the economy £40 million each year. These numbers become bigger when examining the effects in the long run. Table 13 summarises the results.[184]

Table 13: Avoidable productivity losses in England from intensive glucose control in T1D

	DURING THE FIRST FIVE YEARS		IN THE LONG RUN	
Annual average	*Absolute numbers*	*In value (million)*	*Absolute numbers*	*In value (million)*
Avoidable deaths	10	£10	400	£450
Avoidable YYL	400	--	12,500	--
Avoidable discounted DALYs or QALY gains	1,400	£40	16,500	£ 450

Source: Airoldi, et al. (2006), 'Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes', LSE Working Paper, 2046-4614

THE BENEFITS OF DIABETES DRUGS ACHIEVED IN CHINA

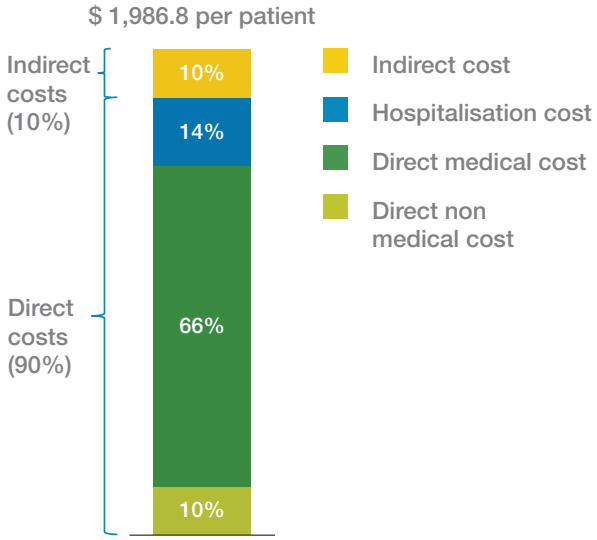
Similar estimates of the economic burden of diabetes have been undertaken in China. Compared to HICs, the economic burden of diabetes in China largely comes from direct costs. As shown in Figure 32, indirect costs, which include productivity loss, account for around 10% of the average annual cost per diabetic patient in China. This is a much lower proportion than that of Canada, where indirect cost accounts for 67% of diabetes' economic burden.[185]

183 For the proposes of the study, the authors consider type 1 diabetes patients to be receiving intensive therapy if: insulin is administered at least three times a day (or with an insulin pump); insulin dosage, dietary intake and exercise adjustment according to results of self-monitoring of blood glucose; self-monitoring of blood glucose is administered at least four times per day; there is a monthly measurement of HbA1c, a monthly visit at the diabetic centre, and specialist calls during the month to review regimens.

184 Airoldi, et al. (2006), 'Estimating health and productivity gains in England from intensive glucose control in Type 1 diabetes', LSE Working Paper, 2046-4614.

185 Canadian Diabetes Association (2009), 'An economic tsunami. The cost of diabetes in Canada'.

Figure 32: Average annual cost per patient with diabetes in China, in USD, 2007



Source: Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', The American Journal of Managed Care, 15,9

Therapeutic/Clinical benefits

There is little evidence, in terms of ex post studies evidencing the reduction in morbidity or mortality, available in MICs or in China specifically.

Clinical trials assessing the effectiveness of diabetes drugs within Chinese patients show that appropriate management of diabetes could bring clinical benefits to the Chinese society.

- A study among T2D patients in China suggested that screening for T2D could reduce microvascular disease by 25%, with a greater reduction in people with good glycaemic control (A1C value greater than 9%).[186]

- A study with sponsorship from Novo Nordisk projected the long-term (30 years) cost of converting patients who were also on OADs from insulin glargine to insulin detemir in China. The study found that the switch would increase patients' life expectancy by 0.06 years (an increase from 11.46 years to 11.52 years) and 0.48 quality-adjusted life years. Perhaps more significantly, the switch is projected to reduce end-stage renal complications by 6.37%.[187]

- A study in China examined the effect of switching patients from biphasic human insulin to biphasic insulin aspart 30. The study found that the switch improved discounted life expectancy by 0.38 years per patient (9.91 years vs. 9.53 years) and quality-adjusted life expectancy by 0.91 years (6.32 vs. 5.41).[188]

186 Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', American Journal of Managed Care, 15,9.

187 Yang et al (2012), 'Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study', Value in Health, 15: S56-S59.

188 Palmer et al (2008), 'Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China', Adv Ther 25(8): 752-774.

Controlling costs in the healthcare system

Studies have found that effective use of diabetes treatments could lead to significant healthcare savings in China:

- Wang et al (2009) estimated that if 95% of T2D patients adhered to metformin therapy it could result in $6.4 billion in savings of direct costs by 2030. Screening for T2D in the general population, having glycaemic control among patients with A1C levels over 8%, and controlling blood pressure could save at least $1,309 in annual direct medical costs.[189]

- One of the major diabetes manufacturers reported that the lifetime cost of treatment and management of T2D patients with diabetes under control is higher than that of patients whose diabetes is not under control (105,000 DKK vs. 84,000 DKK), however, the lifetime cost of complications is lower for those whose T2D is under control (49,000 DKK vs. 66,000 DKK).[190]

- A study projected the long-term (30 years) cost of converting patients who were also on oral anti-diabetic drugs (OADs) from insulin glargine to insulin detemir in China. The study found that switching to insulin detemir+OAD from insulin glargine+OAD would increase diabetes drug and management costs by US$400, but decrease the cost of treating complications by US$820. The net savings from switching to insulin detemir was US$420 over a period of 10 years.[191]

- A study in China examined the effect of switching patients from biphasic human insulin to biphasic insulin aspart 30, where the bolus insulin is an insulin analogue rather than human insulin. The study found that the switch increased the total direct medical cost per patient by 1751 CNY, due to higher pharmacy and management costs (+19,007 CNY), which were offset by reduced diabetes-related complication costs (-17,254 CNY). The incremental cost-effectiveness ratio per QALY gained with biphasic insulin aspart 30 compared to biphasic human insulin was 1926 CNY.[192]

Wider benefits to society

Evidence of socio-economic benefits of diabetes therapy in China is still scarce. Although authors acknowledge that the major hazards of diabetes are complications that can result in disability and early death, there is limited evidence quantifying the socio-economic cost that could be avoided if patients were appropriately treated in China. This is likely due, in part, to lower indirect costs (e.g. productivity loss) in China compared to the cost of treatment, unlike in HICs, where indirect costs constitute a fairly large portion of the societal cost of diabetes.

189 Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', American Journal of Managed Care', 15,9.

190 Novo Nordisk (2011), 'Changing diabetes in China', The Blueprint for Change Programme, February 2011.

191 Yang et al (2012), 'Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study', Value in Health 15: S56-S59.

192 Palmer et al (2008), 'Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China', Adv Ther 25(8): 752-774.

- Wang et al (2009) estimated that a 95% adherence to metformin therapy among T2D patients could save between $0.4 and $0.5 billion in indirect costs, which includes lost income by patients and family members and the cost of hiring care providers. The low proportion of indirect cost savings as a proportion of total savings (around 6.9%) is likely due to the high unemployment rate of the study group (more than 83% unemployed) coupled with low individual income (at least 68% with less than $260 monthly income).[193]

- One of the major diabetes manufacturers stated that the improved products and services they provide saved 140,000 life years in 2010, a number that is expected to grow at an annual rate of 30%, reaching more than 500,000 years in 2015. It is also predicted that type 2 diabetics whose diabetes is controlled are expected to have lower lifetime lost productivity compared to those whose diabetes is uncontrolled (34,000 DKK vs. 50,000 DKK).[194]

4.4. THE VALUE OF MEDICINES FOR DIABETES IN HICS AND MICS

Diabetes is a lifelong disease that requires the complex and delicate management of glycaemic control and prevention of acute long-term complications. Studies have shown that appropriate treatment, close monitoring and behavioural changes can delay or prevent the progression.[195] It is one of the most common NCDs in the world, with similar prevalence rates in HICs and MICs as of 2012. However, the number of individuals suffering from diabetes is significantly larger in MICs (around 374 million) compared to HICs (75 million) simply due to relative size of population and the burden is increasing rapidly.

There has been considerable advance in the medicines available for treating diabetes. Diabetes is normally treated by using insulin therapy as a replacement therapy and/or by controlling blood glucose levels with OAD. The IDF recommends metformin as a first-line treatment, and other glucose control agents such as sulphonylurea as a second-line treatment. Newer OADs such as AGI, meglitinides and thiazolidinediones were introduced in the early 1990s, and further innovative agents such as GLP-1 agonists and DPP-4 inhibitors were launched in the mid-2000s.

Diagnosis, treatment and management of diabetes are very well defined in HICs. The access to treatment in MICs appears significantly less complete. Diabetes care in China has limited infrastructure, and the delivery of healthcare varies considerably by location. Additionally, there is a lack of diabetes awareness in China, resulting in relatively low rates of diagnosis – about 10%-15% of people with T2D are diagnosed, compared to a 50% diagnosis rate in Europe.[196] Furthermore, access to monitoring is also limited. The Diabcare-China study of T2D participants showed the following:[197,198]

193 Wang et al (2009), 'Type 2 diabetes mellitus in China: A preventable economic burden', American Journal of Managed Care', 15,9.

194 Novo Nordisk (2011), 'Changing diabetes in China', The Blueprint for Change Programme, February 2011.

195 Wang (2011), 'Diabetes care in China. Impacts of Traditional Chinese Medicine (TCM) and insurance on quality and utilization', dissertation for doctoral degree at the Pardee RAND Graduate School.

196 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

197 The Diabcare-China study collected data from a cohort of 2,700 people with diabetes at 30 specialist centres across China.

198 Pan (2005), 'Diabetes care in China: meeting the challenge', Diabetes Voice, 50,2.

- More than half of the people with diabetes had poor blood glucose control (glycaemic control).

- Half of the people had their HbA1C (an indicator of long-term blood glucose levels) measured in the last 12 months.

- About three in five people with diabetes had poor metabolic control, showing above-average levels of triglycerides and LDL cholesterol (so-called 'bad' cholesterol).

However, insulin and oral hypoglycaemic drugs are included on the Chinese EDL, meaning that some treatments are available. Additionally, the Chinese government has recently launched the Chinese National Plan for Non-Communicable Diseases Prevention and Treatment 2012-2015, which aims to develop a plan for NCD including diabetes.

We found evidence that diabetes therapies have brought value in HICs in terms of clinical benefits and reduction of healthcare costs, as well as wider socio-economic benefits such as the avoidance of DALYs lost. Diabetes treatments have also yielded clinical benefits in China when they were used, and there is evidence that effective treatment results in savings to the health system. Treatment has also been shown to reduce lost productivity among diabetics in China, although since indirect costs were a smaller portion of the societal cost of diabetes in China compared to HICs, the savings per person is not as large. The Table below shows these results.

Table 14: The value of treatment for diabetes: HIC vs. China

	HICS	CHINA
Therapeutic/clinical value	✓	✓
Controlling costs	✓	✓
Wider benefits	✓	Limited

Source: CRA analysis

5

HIV/AIDS

HIV was originally identified as the likely cause of AIDS in the early 1980s, and within the following two decades, HIV/AIDS was recognised as a global health priority. Despite HIV/AIDS being a global epidemic, the biggest challenge was faced by LICs and MICs (particularly in Sub-Saharan Africa).[199]

The aim of this case study is to review the evidence regarding the value that HIV medicines have delivered over the last 25 years and the degree to which this differs between MICs. Given the burden this disease in Africa, we have included Botswana, in addition to Brazil, China, India and South Africa. After briefly reviewing the development of medicines, we have looked at policies applied to control HIV/AIDS, access to antiretroviral therapy (ART), and the evidence on the value that these treatments have delivered.

5.1. EVOLUTION OF TREATMENT OPTIONS FOR HIV/AIDS

HIV/AIDS is a relatively recent disease, being clinically recognised for the first time in 1981.[200] Inevitably, the medicines to address it have been developed relatively recently. Over the last twenty years, a number of new classes of medicines have been developed. In addition, pharmaceutical companies have developed novel drug combinations.

THERAPY OPTIONS FOR THE TREATMENT OF HIV/AIDS

Commercialisation of the first HIV/AIDS medicines started in the mid-to-late 1980s with the release of zidovudine, the first in class nucleoside reverse-transcriptase inhibitor. The treatment paradigm for HIV/AIDS was developed in the mid-1990s when a new generation of antiretroviral drugs became available. This was followed by the introduction of protease inhibitors (PI) and non-nucleoside reverse-transcriptase inhibitors (NNRTI). The new drugs in combined therapy with the older nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI) reduced the development of virus resistance to the medication, which had been one of the main limitations to the long-term efficacy of antiretroviral monotherapy.[201] This kind of combined treatment is known as Highly Active Antiretroviral Therapy (HAART). Current first-line HAART typically comprises 2 NRTIs plus 1 NNRTI or alternatively 2 NRTIs plus 1 PI (usually a ritonavir-boosted PI) and should not be confused with fixed-dose combination (described below). This is summarised in Figure 33.

Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life cycle that the drug inhibits:

- **Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)** inhibit reverse transcription by being incorporated into the newly synthesised viral DNA strand as a faulty nucleotide. This causes a chemical reaction resulting in DNA chain termination.[202] Examples of NRTIs include tenofovir and zidovudine.

199 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

200 Gallo R (2006) 'A reflection on HIV/AIDS research after 25 years', Retrovirology, 3,72.

201 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

202 Das and Arnold (2013), 'HIV-1 reverse transcriptase and antiviral drug resistance. Part 1', Current Opinion in Virology, 3, 2.

- **Non-nucleoside reverse transcriptase inhibitors (NNRTI)** inhibit reverse transcriptase directly by binding to the enzyme and interfering with its function. Examples of NNRTIs include nevirapine and efavirenz.[203]

- **Protease inhibitors (PIs)** target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new virions. Examples of PIs include atazanavir, ritanovir and lopinavir. Ritonavir is often used to boost other PIs.

- **Integrase inhibitors** inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell (an important step for viral replication). There are several integrase inhibitors currently under clinical trial, and raltegravir became the first to receive FDA approval in October 2007. This includes raltegravir, elvitegravir and dolutegravir .[204]

- **Entry inhibitors (or fusion inhibitors)** targets the initiation processes of the viral infection by interfering with the binding, fusion and entry process of HIV-1 to the host cell by blocking one of several targets. Two molecules, maraviroc and enfuvirtide, are the only two entry inhibitors that are currently available.[205]

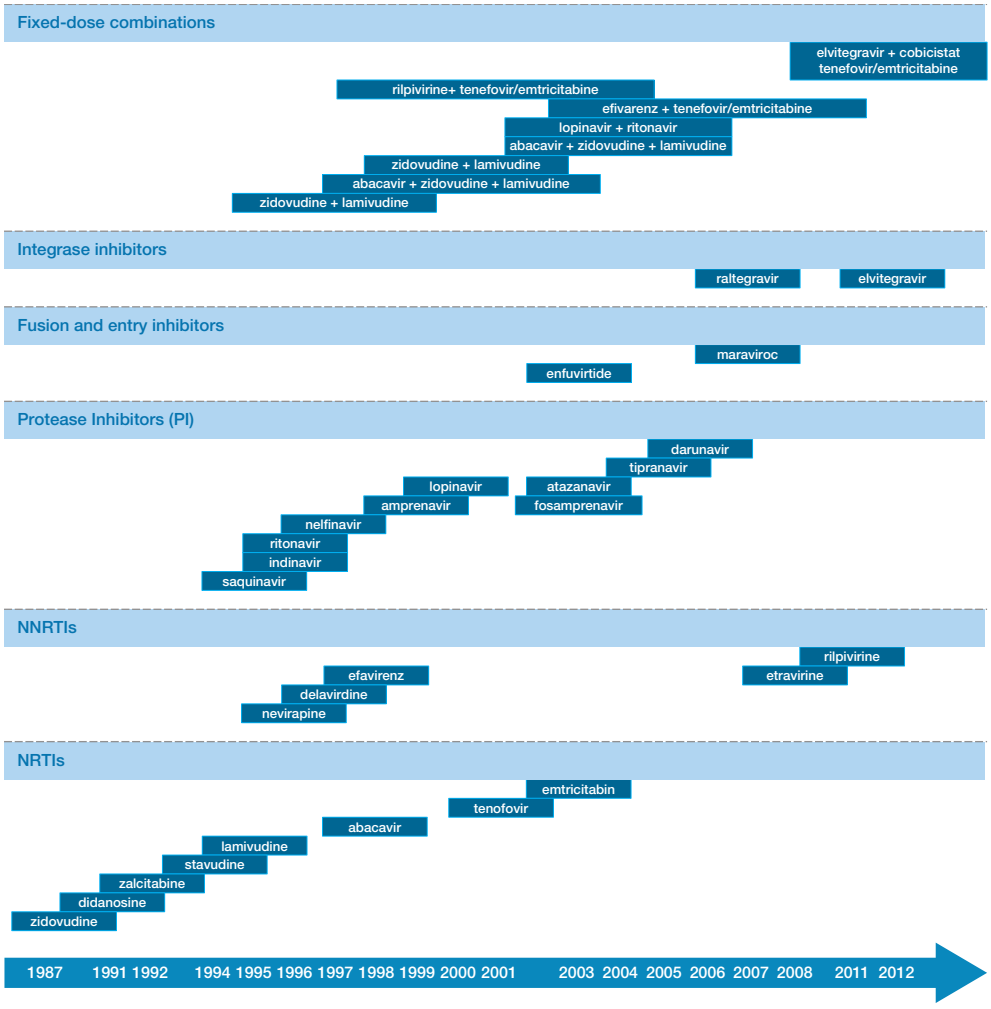
- **Fixed-dose combination (FDC)** with respect to ART refers to a pill that combines two or more ARVs into a single-dose pill. Combinations may also include ritonavir-boosted PIs, where the ritonavir is used in conjunction with another PI to boost the effect of the latter. Examples include efavirenz + tenofovir + emtricitabine, zidovudine + lamivudine and lopinavir + ritonavir (the latter is ritonavir-boosted PI).

203 Das and Arnold (2013), 'HIV-1 reverse transcriptase and antiviral drug resistance. Part 1', Current Opinion in Virology, 3, 2.

204 Kessl, et al (2012), 'Multimode, Cooperative Mechanism of Action of Allosteric HIV-1 Integrase Inhibitors', Journal of Biological Chemistry, 287, 20.

205 De Feo and Weiss (2012), 'Escape from Human Immunodeficiency Virus Type 1 (HIV-1) Entry Inhibitors', Viruses, 4, 12.

Figure 33: First appearance of novel treatment classes of ARV drugs



Source: CRA analysis using Decision resources HIV product portfolio Note: these are the individual stand-alone products. Approved drug combination therapy is not included in this timeline. NRTI – Nucleoside and nucleotide reverse transcriptase inhibitors; NNRTI – Non-nucleoside reverse transcriptase inhibitors

The development of HIV/AIDS drugs can be said to have involved both incremental and radical innovative activities.

RECOMMENDED TREATMENT FOR HIV/AIDS IN WHO GUIDELINES

Since the first WHO guidelines for HIV/AIDS treatment were published in 2002, ARV drugs for first – and second-line treatments have been revised three times. Regular updates of treatment guidelines are an expected consequence of the significant advances made by researchers in the field over the last several years.[206] Changes in first-line ARVs recommended by WHO are displayed in Figure 34.

- The **first WHO HIV/AIDS guidelines** were released in 2002. WHO recommended seven regimens, all of which were based on the use of zidovudine, the first NRTI, which became available in the late '80s, and lamivudine. Different types of combinations were also recommended: 3 NRTIs, 2 NRTIs plus 1 NNRTI, and 2 NRTIs plus 1 PI.

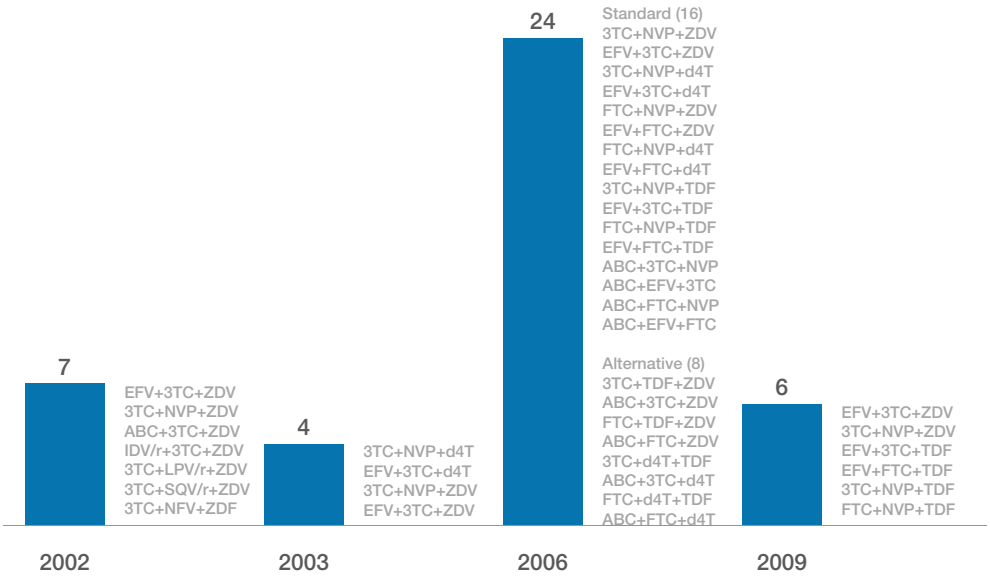
206 Waning et al. (2010). 'Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets', Globalization and Health, 6,9.

- The **first revision of WHO guidelines**, published in 2003, reduced the number of recommended first-line treatments to four combinations of the same type, 2 NRTIs plus 1 NRT. It also incorporated stavudine-based combinations and the use of efavirenz, another NNRTI. PIs were also excluded from first-line treatments in the 2003 guidelines.

- In 2006, a **second revision of WHO guidelines** was released, which included 16 standard regimens and 8 additional alternative regimens, almost all of which utilised 2 NRTIs plus 1 NRTI. This revision incorporated two new NRTIs, emtricitabine and tenofovir. The 2006 guidelines also suggested moving away from older regimens due to related toxicities.

- Finally, a **third revision of WHO guidelines**, reduced the number of recommended first-line treatments to just six combinations, excluding stavudine-based treatments.[207],[208]

Figure 34: Recommended first-line ART in WHO guidelines



Source: Waning et al. (2010). 'Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets', Globalization and Health, 6, 9. Note: EFV – efavirenz, 3TC – lamivudine, ZDV – zidovudine, NVP – nevirapine, ABC – abacavir, IDV/r – indinavir/ritonavir, LPV/r – lopinavir/ritonavir, SQV/r saquinavir/ritonavir, d4T – stavudine, FTC – emtricitabine, TDF – tenofovir

The guidelines have further been update in 2013.[209] The largest change in the new recommendations is to encourage all countries to initiate treatment in adults living with HIV when their CD4 cell count falls to 500 cells/mm^3 or less.[210] They report that, as at 2013, 90% of all countries have adopted the 2010 recommendation.

As discussed, HIV/AIDS detection, treatment and monitoring pathways have been widely defined. To illustrate how this is meant to be applied we use the patient treatment pathway followed in Botswana to illustrate the steps that are typically recommended within MICs.

207 Waning et al. (2010). 'Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets', Globalization and Health, 6(9).

208 WHO (2010) 'Antiretroviral therapy for HIV infection in adults and adolescents – Recommendations for a public health approach 2010 revision', World Health Organization.

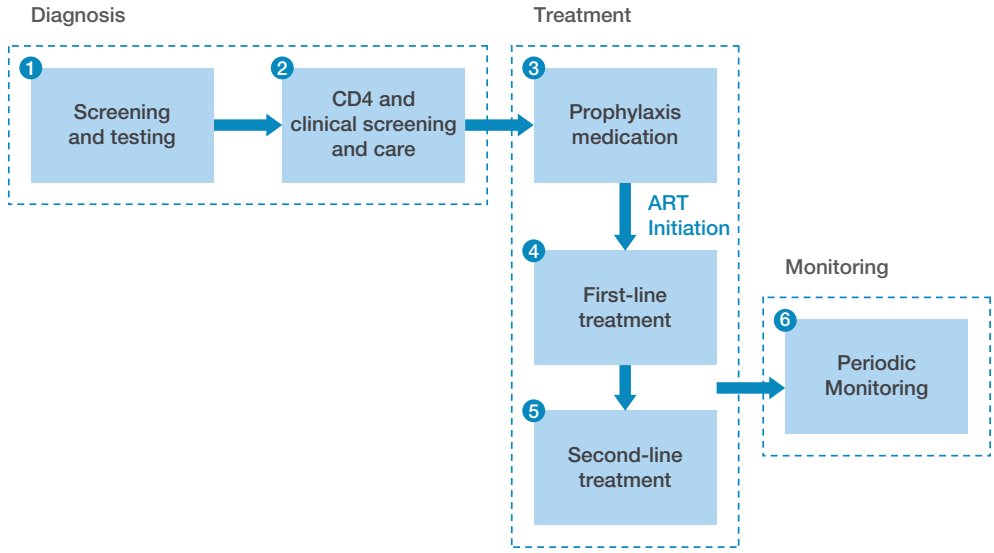
209 "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" available at http://www.who.int/hiv/pub/guidelines/arv2013/en/

210 The previous WHO recommendation, set in 2010, was to offer treatment at 350 CD4 cells/mm^3 or less.

In Botswana, patients are first screened and tested using the 'double rapid' or ELISA test; this should be available in all clinical and outreach settings throughout the country. Patients diagnosed with HIV/AIDS should promptly have CD4 and clinical screening to determine eligibility for ART and other opportunistic infection medication (patients with severe cases of HIV/AIDS will be given prophylaxis medicines against other pathogens).[211]

Patients eligible for ART commence first-line treatment, which includes two NRTIs and one NNRTI.[212] If patients are intolerant of the NNRTI, they are switched to a PI whose selection is based on various criteria. Patients who fail first-line treatment are placed on second-line treatment. Again, this follows WHO 2010 guidelines and includes two NRTIs and one NNRTI. During the first two years of ART, patients are monitored carefully and are scheduled for a check-up every three months. These steps are summarised in Figure 35.

Figure 35: HIV/AIDS treatment pathway in Botswana



Source: Botswana Ministry of Health (2012) Botswana National HIV & AIDS treatment guidelines

5.2. ACCESS TO MEDICINES FOR HIV/AIDS

In order to be able to determine if innovation in the treatment of HIV/AIDS has brought benefits in MICs it is important to see if the current treatments are actually available and accessible in these markets. In this section, we summarise the national strategies introduced by the selected MICs to fight against HIV/AIDS and then look at the access of HIV/AIDS treatments in MICs.[213]

211 Botswana Ministry of Health (2012) 'Botswana National HIV & AIDS treatment guidelines'.

212 These are the class combinations recommended by WHO in its 2010 guidelines.

213 Access data in MICs has some key country data missing, including China and India.

NATIONAL STRATEGIES APPLIED TO CONTROL HIV/AIDS

HIV/AIDS has been of great concern within MICs, leading governments to introduce and implement specific national HIV/AIDS strategies. Although different policies have been applied, all governments had a similar goal: to control the HIV/AIDS epidemic by preventing transmission and providing access to treatment. In this report we focus on specific MICs that have responded to the HIV/AIDS threats by introducing national policies to improve the situation; these include Botswana, Brazil, China, India and South Africa.

- In 1999 the President of the Republic of Botswana declared HIV/AIDS to be a national emergency. Shortly after, in 2001, Botswana became the first country in Africa to offer ARVs to any of its affected citizens through the public health system. This involved considerable investment, the majority being domestic. It is estimated that the government contributes 2-3% of GDP to support AIDS prevention, care and treatment; this amount constitutes 80-90% of the required resources for treatment.[214] In 2004 Botswana introduced routine HIV/AIDS testing with all hospital visits. Additionally, Botswana participated in the African Comprehensive HIV/AIDS Partnerships (ACHAP), formed in 1999, which continuously received funding.

- In Brazil, a nationwide ART distribution programme was originally put in place by the Ministry of Health in 1986. It was then established as part of the Brazilian Constitution of 1988. In 1996, a federal law was introduced stating that all patients suffering from HIV/AIDS and in need of treatment should receive it free of charge. The main source of funding for Brazil's response to the HIV/AIDS epidemic was domestic; however, between 1993 and 2007 Brazil received three loans from the World Bank to strengthen its health system by training healthcare professionals, purchasing equipment and starting prevention campaigns.[215]

- China recognised that an HIV/AIDS epidemic would cause consequences to economic well-being, quality of life and mortality. In 2003, China launched its first five-year action plan: 'Four Frees and One Care' policy providing access to free HIV testing, ART and prevention of HIV mother-to-child transmission. In China, domestic funds account for the largest majority of HIV/AIDS funding within the country.[216],[217]

- India has had an HIV/AIDS programme since the 1980s and created the National AIDS Control Organisation (NACO) in the early 1990s which focused on preventive strategies.[218] The implementation of a universal treatment programme for HIV/AIDS did not occur until 2004. That year, the government of India initiated a universal public ART programme, through which first-line ARVs were provided to the

214 Rook (2009), 'Public-Private Partnerships in the Fight Against HIV/AIDS: A Case Study of Botswana', School of Public, Nonprofit and Health Administration Review, 5, 1.

215 Galvao et al. (2008), 'How the pandemic shapes the public health response — the case of HIV/AIDS in Brazil', Public Health Aspects of HIV/AIDS in Low and Middle Income Countries.

216 Sun et al. (2010), 'Evolution of information-driven HIV/AIDS policies in China', International Journal of Epidemiology, 39:ii4–ii13.

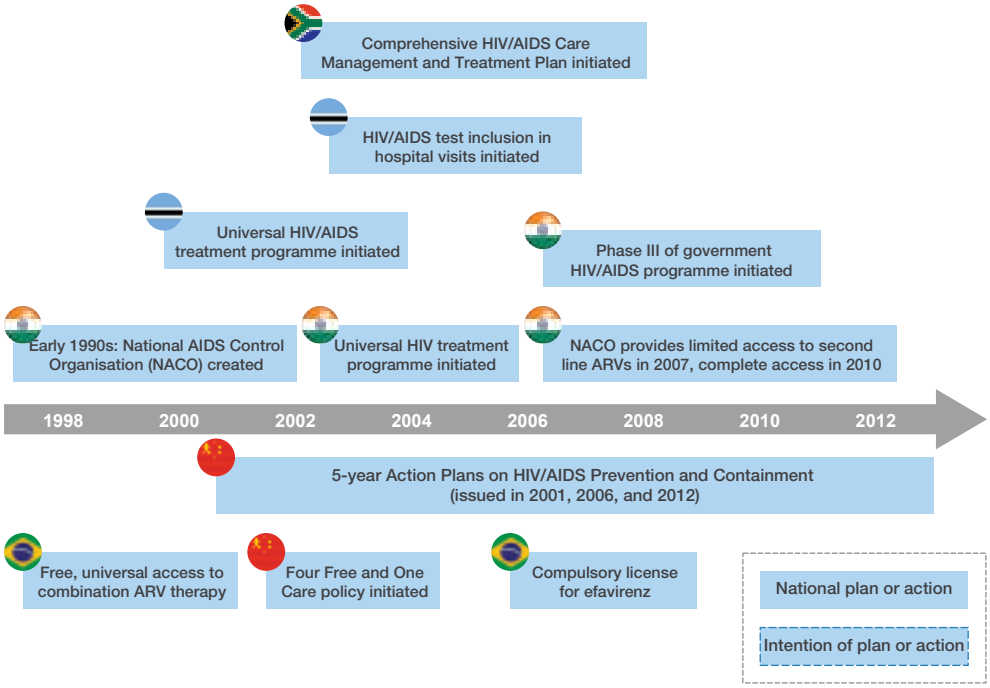
217 Wu et al. (2010) 'China AIDS policy implementation: reversing the HIV/AIDS epidemic by 2015', International Journal of Epidemiology; 39:ii1–ii3.

218 AVERT (2011), 'Overview of HIV and AIDS in India,' accessible at http://www.avert.org/AIDSindia.htm.

infected population at eight health centres in six of the highest prevalence states and the capital (by 2008, 137 centres in 31 states provided ART).[219] Towards the end of 2010, the Supreme Court of India ordered NACO to provide second-line treatment to the entire population, regardless of wealth or site of prior first-line treatment.[220] NACO has a budget of approximately $2.6 billion, of which the majority is used for prevention efforts and only one-sixth for treatment. Funding comes from a mixture of different origins, including the Indian government, international organisations such as the World Bank, and the Bill and Melinda Gates Foundation.[221]

- The 'Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa' was established in 2003 and launched in 2004.[222] This was the start of a detailed operation plan on antiretroviral treatment setting out a comprehensive strategy on how to deal with the HIV/AIDS epidemic.[223] The new Comprehensive HIV/AIDS Care, Management and Treatment Plan included a provision for all patients attending public health facilities with a CD4+ count <200 cells/mm3 to receive ART.[224] The South African government has been responsible for providing a large amount of the funds used. In 2006, public funds accounted for $425.9 million of HIV/AIDS spending, and public spending has increased each year since then, accounting for $1.5 billion in 2009.[225]

Figure 36: Timeline of national strategies against HIV/AIDS in BICS + Botswana



Source: CRA analysis

219 UNGASS (2010) 'Country Progress Report — India'. United Nations General Assembly Special Session (UNGASS).

220 Hindustan Times (2010), 'SC Cautions Government Over HIV Treatment' December 11.

221 Kaiser Family Foundation (2006), 'India Primarily to Promote Condom Use in its HIV Prevention Programs, Health Minister Says' September 5.

222 Government of South Africa (2003), 'Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa', available at http://www.info.gov.za/otherdocs/2003/AIDSplan/report.pdf.

223 Wouters, et al (2010), 'Who is accessing public-sector anti-retroviral treatment in the Free State, South Africa? An exploratory study of the first three years of programme implementation', BioMed Central, 10, 387.

224 Johnson (2009) 'Access to Antiretroviral Treatment in Adults,' University of Cape Town.

225 CRA analysis using UNAIDS data repository.

THE INTRODUCTION OF ARTS IN THE EDL

Looking at the BRICS we found that HIV/AIDS drugs have been included in their EDL since the very early stage of their design, including at least a molecule for each therapeutic class.

Table 15: Year of introduction of molecules used for the treatment of HIV/AIDS in BICS + Botswana

	BOTSWANA	BRAZIL	INDIA	CHINA+	SOUTH AFRICA
NTRIs	2005	2000	2003	2005	2006
NNRTIs	2005	2002	2003	2005	2006
PIs	2005	2000	2003	2003	2006
Integrase Inhibitor	N/A	2012	N/A	N/A	N/A
Fusion and entry inhibitors	N/A	N/A	N/A	N/A	N/A
Fixed-dose combinations	2005	2002	2003	2005	2006

Source: CRA analysis country specific EDLs. Note: *Indicates that the molecule was introduced but is not included in the 2012 EDL; +ARVs are not included on the Chinese EDL as Anti-AIDS medicines are provided by the government for free to treat HIV/AIDS, the year reflect the introduction of the class within the 'Four Free and One Care' program

Though China doesn't include ARV on its EDL, through the Chinese 'Four Free and One Care' policy, in 2005 (two years after the introduction of the policy), China's first-line regimen followed the WHO guideline, comprising zidovudine or stavudine + lamivudine or difanosine + nervirapine or efavirenz (two NTRIs and one NNRTI).[226,227] Limited amounts of combinations of zidovudine + lamivudine and of efavirenz are also available.[228]

THE EXISTING EVIDENCE ON ACCESS TO HIV/AIDS TREATMENTS IN MICS

International organisations such as UNAIDS and WHO, as well as academic researchers, have developed studies or surveys to determine the extent to which ART are used for the treatment of HIV/AIDS within MICs. As described above, in order to control the HIV/AIDS epidemic countries began launching national strategies based on prevention mechanisms and enhancing treatment options. Here we discuss access of ART in MICs and then more specifically in the selected group of MICs.

Access to ART treatment within MICs

The most widely used measure of access is the ART coverage rate; it is the indicator recommended by the United Nations General Assembly Special Session on HIV/AIDS (UNGASS). Coverage is determined by the fraction of people eligible for ART who

226 Zhang et al. (2005), 'Current progress of China's free ART program', Cell Research, 15, 877–882.

227 Xing et al. (2013), 'HIV Drug Resistance and Its Impact on Antiretroviral Therapy in Chinese HIV-Infected Patients', PLOS ONE, 8, 2.

228 WHO (2005), 'Summary country profile for HIV/AIDS treatment scale-up', WHO publication.

receive effective treatment. This provides an informative perspective on the relative position of countries in their pursuits of universal access as well as the changes in each country over time. However, the measure provides an incomplete representation of the true level of access to ART, and it is highly dependent on each country's definition of need for treatment:

- ART can include a wide variety of combinations of ARV drugs; however, due to different tolerability profiles, or perhaps due to the development of resistance, HIV/AIDS patients may need to receive specific combinations. The wrong combination of ARV drugs can have significant consequences for patients, for example, by accelerating resistance.

- HIV/AIDS patients are typically assessed by looking primarily at the CD4 cell count. The threshold below which ART should be initiated is established by treatment guidelines (which have recently been updated again). The immediate consequence of the change has been an increase in the number of people eligible for ART, and subsequently coverage rates (compared to reported figures in previous years) have fallen.

- The CD4 cell count at which ART is initiated has an impact on the success of treatment to reduce morbidity and avoid mortality. Early initiation of ART after the CD4 cell count falls below the relevant threshold is an important dimension of universal access to ART.

- Continuity and adherence to treatment is necessary to minimise the likelihood of patients developing resistance to treatments. ART coverage rates do not take into account adequate monitoring and support of patients receiving ART as a component of effective access.

In 2011, 50% of HIV patients within MICs were covered with ARTs; the figure was 62% in Latin America. Looking at both the MIC aggregate and the different regions, the percentage of patients covered with ART significantly increased since 2009, with Africa leading the increase in the proportion of patients covered with ARTs.[229]

Access to ART treatment within selected MICs

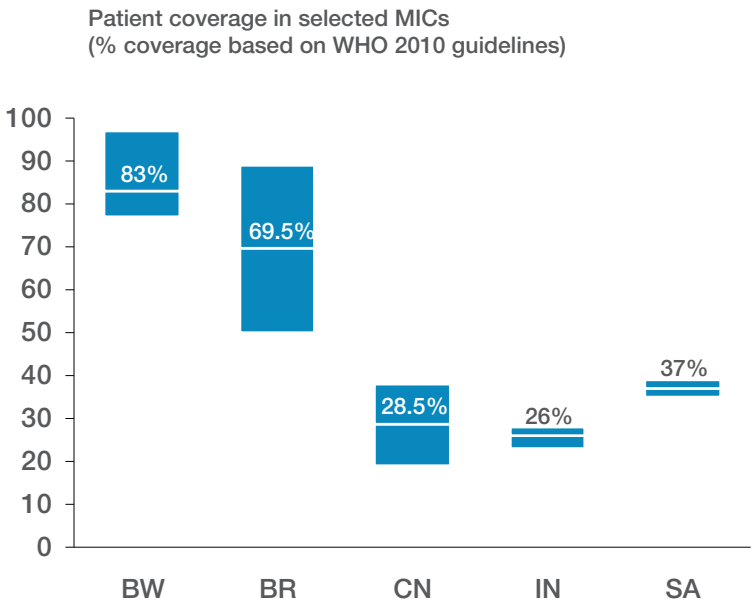
From the data available, we can see that the introduction of the national policies previously described has contributed significantly to the increase in access to ART in the selected MICs. Every country has seen a large rise in the population receiving treatment, and in all countries this continues to grow significantly year on year. If the selected MICs continue such growth, they will attain universal access and therefore access will no longer be a limiting factor to the benefits of ART.

By the end of 2009, eight MICs had achieved universal access to ART (described as providing therapy to more than 80% of patients who required it). This included Botswana. 21 additional LIC/MICs reported coverage rates greater than 50% (including Brazil)

229 CRA Analysis using UNAIDS data repository. Note: China and India do not have data on coverage in the UNAIDS data repository, and Russia has data missing for 2011. Various other countries also lack data.

based on WHO 2010 treatment eligibility criteria.[230] Figure 37 illustrates the level of coverage in the selected MICs. The figure shows the disparity between the selected MICs and their level of coverage.

Figure 37: Use of medication in patients with HIV/AIDS by country, with upper and lower bounds, 2009



Patient coverage in selected MICs (% coverage based on WHO 2010 guidelines with ranges)

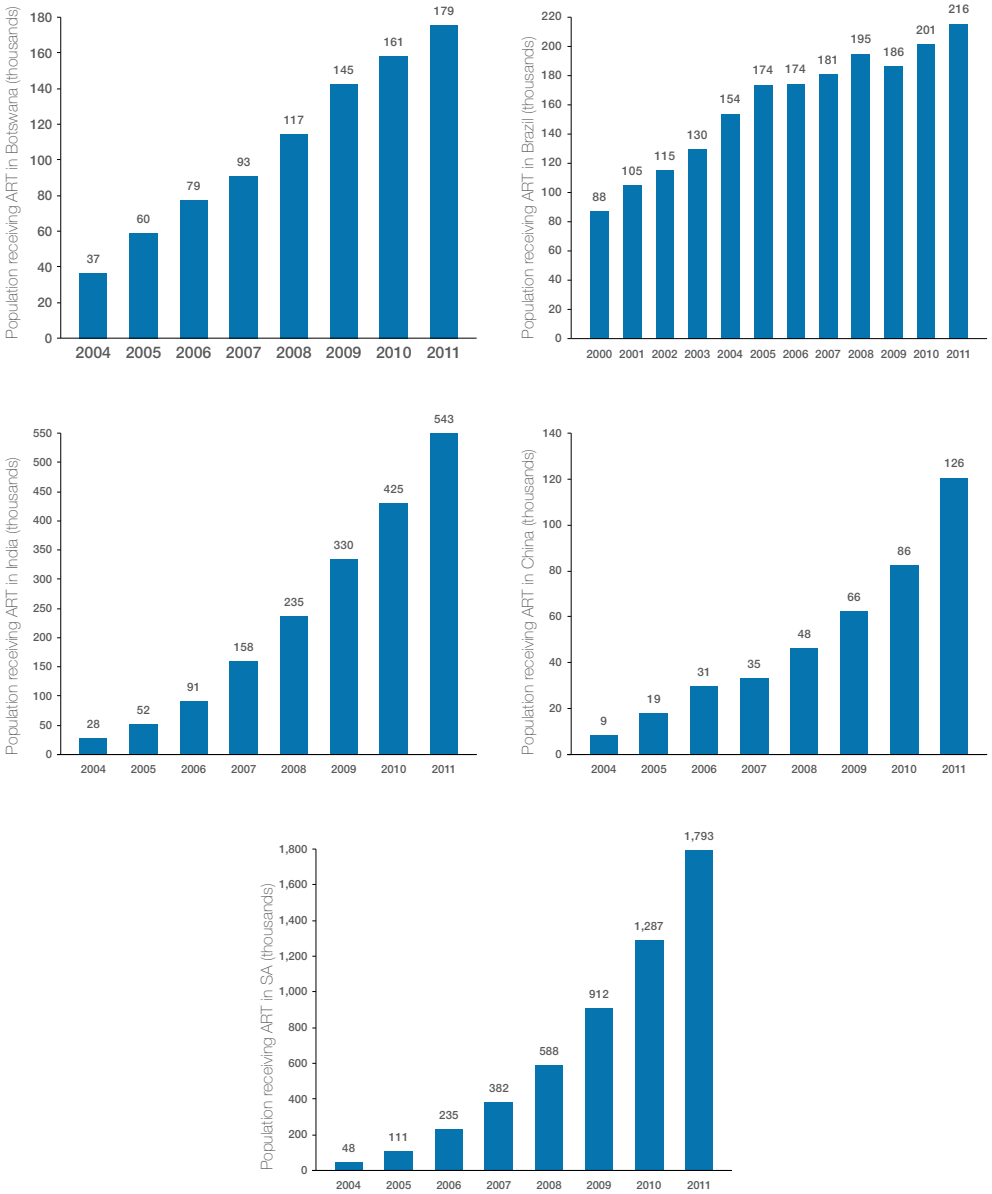
Country	Estimated	Lower bound range	Upper bound range
BW	83.0%	77.0%	97.0%
BR	69.5%	50.0%	89.0%
CN	28.5%	19.0%	38.0%
IN	26.0%	23.0%	28.0%
SA	37.0%	35.0%	39.0%

Source: CRA analysis country specific EDLs. Note: Botswana (BW), Brazil (BR), China (CN), India (IN), South Africa (SA); *Indicates that the molecule was introduced but is not included in the 2012 EDL; +ARVs are not included on the Chinese EDL as Anti-AIDS medicines are provided by the government for free to treat HIV/AIDS, the year reflect the introduction of the class within the 'Four Free and One Care' program

When we looked at time series data on the population receiving ART treatment, we found that access to ARTs has improved significantly across all the selected countries. This is shown in Figure 38.

230 WHO, UNAIDS, UNICEF (2010) 'Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector', a WHO report.

Figure 38: Uptake of ART treatment (thousands) in the selected countries



Source: CRA Analysis using UNAIDS data repository

Access to FDC

Data looking at the level uptake of FDC across the selected countries is scarce. However, as shown in Table 15, all countries have included FDC in their EDL. South Africa is an exception as the FDC available was a ritonavir-boosted PI rather than a combination of different ARVs, but recent regulatory changes in the country stated that the provision of FDC products would be available as of April 2013.[231]

231 SA news, 'SA making progress in tackling HIV – Motlanthe' viewed at http://www.sanews.gov.za/south-africa/sa-making-progress-tackling-hiv-%E2%80%93-motlanthe.

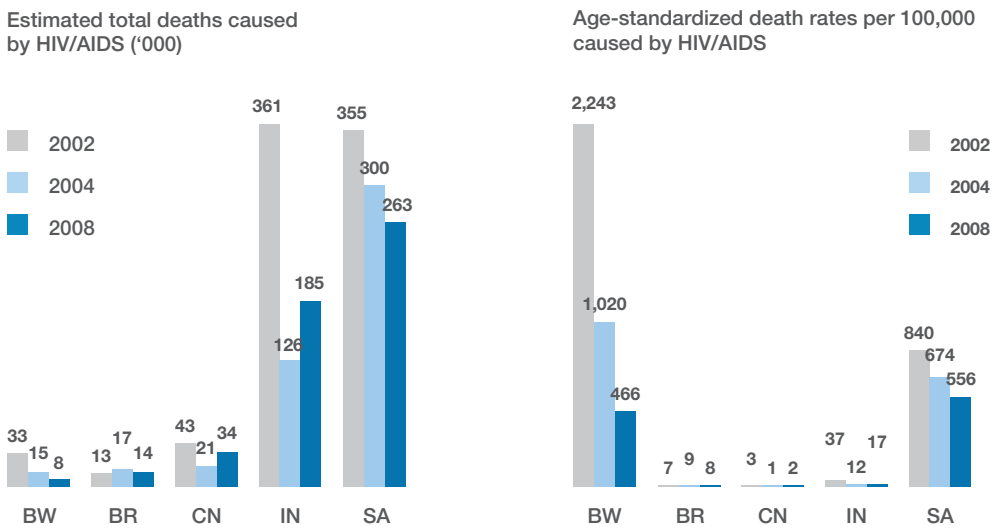
Turning to the existing evidence on the value that ARTs have brought within MICs and in particular within the selected countries we find this is extensive.

THERAPEUTIC/CLINICAL BENEFITS

The mortality rates associated with HIV/AIDS have decreased within all the selected countries. As shown in Figure 39, all countries have seen a reduction in the number of deaths due to HIV/AIDS from 2002 to 2008.While India has the largest absolute reduction in the total number of deaths, the largest percentage reduction is in Botswana.

As HIV/AIDS has been transitioned to a more chronic disease, it is possible that number of DALYs could increase even if mortality has decreased. However, DALYs also show a general decrease throughout the countries.

Figure 39: Burden of HIV/AIDS within selected MIC



Source: CRA analysis using WHO Statistical Information System (WHOSIS), Global burden of disease. Available here http://www.who.int/healthinfo/global_burden_disease/gbd/en/index.html Last accessed: July 2013. Note: Botswana (BW) Brazil (BR), India (IN), China (CN), South Africa (SA)

The reduction of the burden of HIV/AIDS within these markets is aligned with an improvement in access to ARTs. The relation between the use of ARTs and the reduction of the burden of disease has been demonstrated in literature:

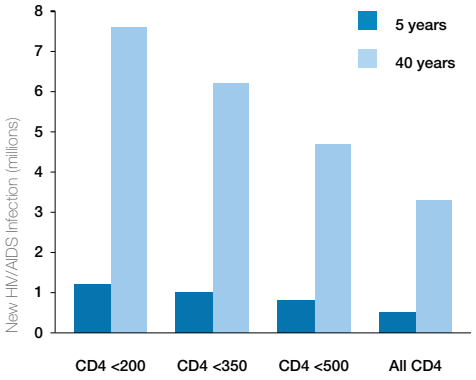
- In Brazil the World Bank stated that due to changes in policy that promoted both prevention and access to innovative treatment, the number of people living with HIV/AIDS was reduced by 60% in relation to the affected population in the early '90s.[232]

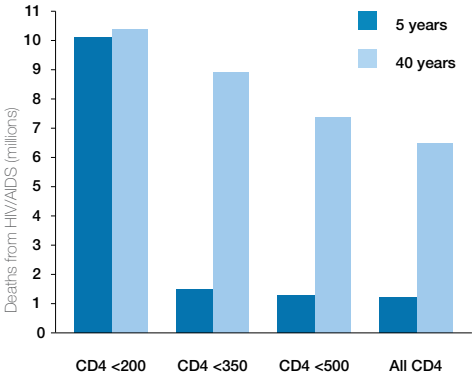
- In South Africa a study conducted by Granich et al. (2012) demonstrated that there are almost instantaneous benefits to an expansion in ART coverage such

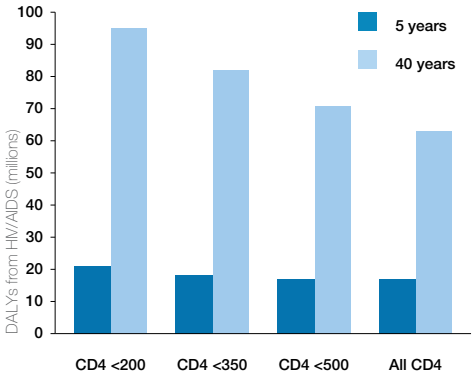
232 Greco D, Simao M (2007) 'Brazilian policy of universal access to AIDS treatment: sustainability challenges and perspectives', WHO report.

as the one in WHO 2010 guidelines over WHO 2006.[233] The study models the estimated new HIV/AIDS infections, deaths, and DALYs lost for several different coverage scenarios. The authors show that if HIV/AIDS patients with any CD4 amount are placed on ART immediately, rather than after exhibiting a specific CD4 cell amount, after just 5 years there would be 700,000 fewer new infections than if the 2006 WHO guidelines were being practiced. There would also be significantly fewer deaths, with 8.9 million more surviving the following 5 years and a reduction in DALYs lost of 4 million. This is summarised in Figure 40 with the total difference between the highest coverage scenario and the baseline scenario.[234]

Figure 40: Therapeutic and clinical benefits of increasing ART coverage criteria in South Africa







Difference between baseline (CD4 <200) and other scenarios (difference in millions)

	CD4 <350		CD4 <500		All CD4	
	5 yr.	40 yr.	5 yr.	40 yr.	5 yr.	40 yr.
New HIV infections difference	-0.2	-1.4	-0.4	-2.9	-0.7	-4.3
Deaths difference	-8.6	-1.5	-8.8	-3	-8.9	-3.9
DALYs difference	-3	-13	-4	-24	-4	-32

Source: Granich R et al. (2012) Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050, PLOS ONE, Vol. 7, no. 2. Note: All CD4 levels scenario involves offering ART to everyone immediately after diagnosis with HIV irrespective of CD4 count

- A recent study assessing the National Free Antiretroviral Treatment Program (NFATP) in China also showed how mortality rates in HIV patients fell sharply among people receiving antiretroviral therapy between 2003 and 2009. Overall, people were about 30% less likely to die in the period 2008-09 compared to 2003-04, before the program expanded.[235]

233 Expansion from CD4+ <200 cells/mm^3 (WHO 2006).

234 Granich R et al. (2012) 'Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050', PLOS ONE, 7, 2.

235 Zhu et al (2013), 'Decreasing excess mortality of HIV-infected patients initiating antiretroviral therapy: comparison with mortality in general population in China, 2003-2009', Journal of Acquired Immune Deficiency Syndromes, 10.

In addition, the benefit of ART is increasingly viewed in the context of preventing HIV transmission rather than that of treatment alone. ART plays a crucial role in the prevention of mother to-child transmission (PMTCT). In 2009, an estimated 370,000 children contracted HIV during the perinatal or breastfeeding period, down from 500,000 in 2001, largely thanks to the use of PMTCT ART. In some countries like South Africa, coverage for PMTCT has reached 90%, which has drastically reduced the transmission to children from a peak of over 200,000 in 2004 to fewer than 100,000 in 2011.[236,237]

We searched for studies on the value of supplying the population with FDC in the selected countries, but these are limited. A WHO meeting report stated that there is indeed little reliable evidence on the value of FDC in terms of adherence (or treatment outcomes) in HIV/AIDS.[238] Although there were articles that speculated that the relative ease of use of such medicines would improve adherence to ART, we have found little empirical evidence of this.

However, studies in HICs have demonstrated the value of FDC in terms of patient adherence. A team studied the differences in adherence between patients using FDC and separate combinations in the US using a large health insurance claims database.[239] Patients using FDC had a higher adherence to the medicines than those taking the drugs separately. It is reasonable to assume that if FDC can improve adherence in an HIC like the US, the benefits would also be mirrored in MICs, where adherence is reportedly similar for ARTs.[240]

This is also supported by a study in Uganda that concluded that patients with HIV/AIDS purchasing generic FDC have higher rates of adherence, which brings clinical benefits.[241] As previously mentioned, South Africa has recently introduced policy to provide access to FDC. Although there is no evidence on its success yet, the move is welcomed by the South African National AIDS council (SANAC), who are optimistic that it will encourage a higher rate of adherence as well as simplifying prescribing, dispensing and monitoring for nurses and pharmacists, and also simplifying procurement and supply chain management.[242,243]

CONTROLLING COSTS IN THE HEALTHCARE SYSTEM

Next we considered if there was evidence that improving therapeutic and clinical aspects can have positive repercussions on the costs incurred by the healthcare system. If patient hospitalisations can be reduced due to new treatment options, the costs

236 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

237 CRA analysis using UNAIDS data repository.

238 WHO, (2003) 'Fixed-Dose Combinations For HIV/AIDS, Tuberculosis, And Malaria', Report of a meeting held 16-18 December 2003, Geneva.

239 Valenti W (2004), 'Expanding Role of Coformulations in the Treatment of HIV Infection: Impact of Fixed-Dose Combinations', Medscape news, 14, (10).

240 Red A, and Biadgilign S (2012), 'Determinants of Adherence to Antiretroviral Therapy among HIV-Infected Patients in Africa', AIDS Research and Treatment.

241 Oyugi J et al. (2007), 'Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda', PubMed, vol. 21, iss. 8, 965 971.

242 SA news (2013), 'SANAC welcomes fixed dose combination ARVs', seen on SAnews.gov.za.

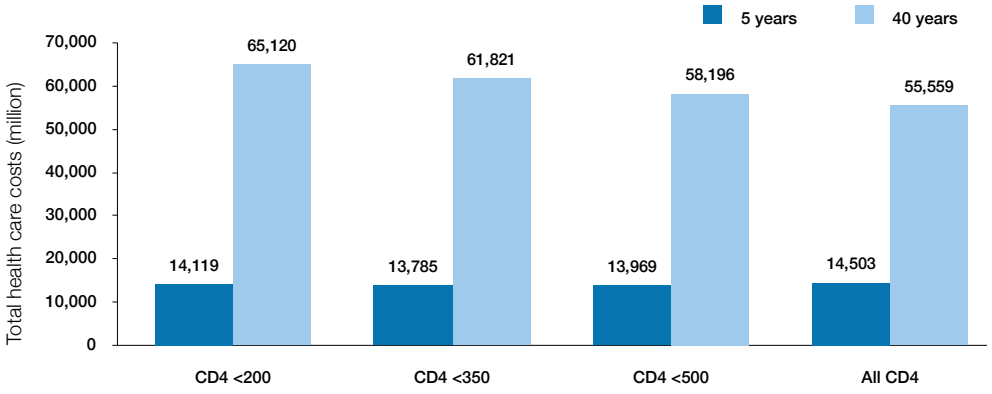
243 South Africa.info (2012), 'Single-dose HIV drug welcomed', seen on SouthAfrica.info.

incurred within the healthcare system will also be reduced, as fewer resources will be consumed. Several studies have assessed the effect of treatment on the overall healthcare costs, proving that access to ARTs lead to a reduction in healthcare costs.

- In Brazil, for example, it is estimated that through the universal provision of ART to patients suffering from HIV/AIDS in 2002, the Brazilian government averted over 60,000 AIDS cases, 90,000 deaths and almost 360,000 AIDS-related hospital admissions, contributing to overall healthcare savings of over $200 million.[244] Additionally, WHO data from Brazil demonstrates that providing universal access to ARTs was cost-effective to the Brazilian government as the estimated cost of providing ARV therapy between 1996 and 2002 was approximately US$1.8 billion, whereas savings achieved through reducing both hospital and ambulatory care services attained $2.2 billion.[245]

- In South Africa a team developed a model that projected the benefits of incremental increases in the coverage of HIV/AIDS. The model found that increases in coverage would lead to significant downstream financial savings. The study, conducted by Granich et al. (2012), demonstrated the benefits with regards to the HIV total cost of care, and modelled the potential savings that extending the treatment eligibility criteria could enable (cost and savings listed in Figure 41). The study compares different eligibility criteria for ART usage, demonstrating how criteria that opens treatment for a larger population has benefits. The study reports that if all patients diagnosed were treated immediately with ARTs, overall costs of HIV care would decrease by $10 billion over a 40-year period, and the breakeven point would be reached by 2023.

Figure 41: Economic effects of extending the ART eligibility criteria in South Africa



Difference between baseline (CD4 <200) and other scenarios (difference in millions)

	CD4 <350		CD4 <500		All CD4	
	5 yr.	40 yr.	5 yr.	40 yr.	5 yr.	40 yr.
Cost savings ($ million)	334	3,299	150	6,924	-384	9,561

Source: Granich R et al. (2012) Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050, PLOS ONE, Vol. 7, no. 2. Note : All CD4 levels scenario involves offering ART to everyone immediately after diagnosis with HIV irrespective of CD4 count

244 Teixeira et al. (2004), 'The Brazilian Experience in Providing Universal Access to Antiretroviral Therapy', Le Publieur, available at http://www.lepublieur.com/anrs/ecoAIDS6.pdf.

245 IRIN Web special (2005), 'Lazarus drug – ARVs in the treatment era', available at http://www.irinnews.org/pdf/in-depth/ARV-era.pdf; Granich et al. (2012), 'Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050', PLOS ONE, 7, 2.

WIDER BENEFITS TO SOCIETY

As with all severe diseases, there is concern over the impact HIV/AIDS has on economic activity, mainly through productivity losses resulting from the inability of an HIV/AIDS patient to stay in the workforce. In South Africa, for example, evidence suggests that AIDS raises the cost of labour and also diminishes the competitiveness of African business in the global marketplace.[246] Indeed, looking at a mining company in South Africa it is estimated that HIV/AIDS can add an additional 4-5% to company costs.[247]

A number of studies have examined the impact of ART treatment on businesses, mainly through the reduction of absenteeism:

- In Botswana a study analysed data of work absenteeism, comparing patients enrolled in one of Africa's first ART programmes and normal healthy workers. The study finds evidence that patients suffering from HIV/AIDS display similar absenteeism patterns as normal healthy workers until one year prior to the start of the treatment. At this point, absenteeism among HIV/AIDS patients increases to a peak of 5 days in the month of treatment onset. Within one year of the programme, the HIV/AIDS patients begin to recover, and for the following few years demonstrate similar patterns to healthy workers. The authors conclude that ARTs are effective in the short, the medium, and the long run with regards to improving both the health and productivity of working patients suffering from HIV/AIDS.[248]

- In India, the impact of ART on socio-economic outcomes was examined using the Tamil Nadu Family Care Continuum program in India. Six months after ART initiation, the patients' participation in the labour force had increased by 26% and the weekly work hours had increased by an average of 14.5 hours.[249]

- In South Africa the experience of a South African employer-based HIV care programme was examined. The analysis found that the short-term savings exceeded costs across all models of employer-based ART provision. The study demonstrated that 2 years after implementation, the net cost per employee decreased from $220 per patient/month to $170 per patient/month. Absenteeism decreased from 7.5 days to 2.9, 2.2 and 2.1 days per month (after 6, 12, and 18 months respectively).[250]

The studies undertaken in Botswana, India and South Africa each show some degree of benefit from the provision of effective treatment to HIV/AIDS patients, indicating that this benefit is not necessarily exclusive to a single country or development level.[251]

246 Rosen et al. (2004),'The cost of HIV/AIDS to business in SA', Official Journal of the International AIDS Society, 18, 2.

247 Du Plessis and Venter (2010), 'HIV/AIDS Is An Epidemic: Empirical Assessment Of The State Of Affairs In A Developing Country', International Review of Business Research Paper, 6, 2.

248 Habyarimana et al. (2009), 'HIV/AIDS, ARV Treatment and Worker Absenteeism: Evidence from a Large African Firm', available at http://www.columbia.edu/~cp2124/papers/arv.pdf.

249 Thirumurthy et al. (2008), 'The impact of antiretroviral therapy on socio-economic outcomes of HIV-infected patients in Tamil Nadu Family Care Continuum program (TNFCC), India', XVII International AIDS Conference.

250 Muirhead et al. (2006), 'Health care costs, savings and productivity benefits resulting from a large employer sponsored ART program in South Africa', XVI International AIDS Conference.

251 According to World Bank data, South Africa and Botswana are classified as UMICs and India is listed as a LMIC.

Socio-economic benefits can also be derived from the perception that patients have of their quality of life. As simpler and more efficacious treatment regimens are becoming more and more available, perceived clinical improvements are no longer limited to improvements in mortality and DALYs, but also pertain to the patient's quality of life. Deterioration in quality of life can be directly related with symptoms of depression and anxiety, which in turn can not only further compromise the immune system but also affect behaviour patterns and negatively influence adherence to treatment due to perceived difficulty of the regimen.[252]

A literature review of various developing countries (including BRICS) studied the effect of ART on quality of life of patients in these countries. The study reported that patients on ART exhibit significant improvement in terms of physical health.[253]

- Brazil – A study on overall quality of life of patients enrolled into the ART programme in Brazil found that after 4 months, 66.4% classified their quality of life as very good or good. The authors made a comparison to another study on HIV patients in Bangalore, India, where the self-perception on quality of life was significantly lower (18% said they had a good quality of life). The authors state that this variance is likely due to the fact that there was free and universal coverage for HIV/AIDS in Brazil at that time, making conditions more favourable for patients in Brazil than in India.[254]

- South Africa – In South Africa (Free State Province), a study assessing the physical and emotional quality of life was undertaken on a population of patients enrolled in the ART programme. The results of the study showed that patients reported overall favourable outcomes in terms of physical and emotional quality of life.[255] Again in South Africa, studies on patients with HIV/AIDS on treatment showed that 86.1% of the patients reported improvements in self-perceived quality of life. It seemed that even qualifying for treatment was perceived as favourable, with 55.3% awaiting ART treatment reporting an improvement in quality of life.[256]

5.4. THE VALUE OF MEDICINES FOR HIV/AIDS IN MICS

HIV/AIDS is a severe disease, and addressing it became a national priority, especially for many MICs (and LICs). Significant steps have been made to address this challenge over the last two decades. The number of people living with the disease is stabilising, and the mortality and DALYs level has decreased significantly both in MICs in general and in the selected MICs. Furthermore, the level of transmission between mother and unborn child has decreased significantly.

252 Campos et al (2009), 'Quality of Life Among HIV-Infected Patients in Brazil after Initiation of Treatment', Clinics, 64, 9.

253 Beard et al. (2008), 'Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review', Boston University Center for International Health and Development, Discussion paper, 11.

254 Campos et al (2009), 'Quality of Life Among HIV-Infected Patients in Brazil after Initiation of Treatment', Clinics, 64, 9.

255 Wouters et al. (2009), 'Physical and emotional health outcomes after 12 months of public-sector antiretroviral treatment in the Free State Province of South Africa: a longitudinal study using structural equation modelling', BioMed Central, 9, 103.

256 Beard et al. (2008), 'Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review', Boston University Center for International Health and Development, Discussion paper, 11.

It is evident that access to ART, in combination with improvement in prevention and diagnosis, has played a significant role. Access to improved FDCs is likely to have had a positive impact in markets where they are available, due to increased adherence.

In addition to clinical and therapeutic benefits, there is also evidence that the introduction of these policies and access to ART is beneficial economically, through reduction in other healthcare costs (such as hospitalisations), and socio-economically, through reduction of absenteeism and improvements in HIV/AIDS patient quality of life. Table 16 provides a summary of the findings within the selected countries.

Table 16: Summary of the findings related to treatment, usage and value of medicines for HIV/AIDS within selected MICs

	BOTSWANA	BRAZIL	CHINA	INDIA	SOUTH AFRICA
National strategy against HIV/AIDS	2001	1986	2003	During 1980s	2004
Inclusion in EDL	Yes except integrase, and fusions and entry inhibitors	Yes except fusions and entry inhibitors	Yes through Free ART	Yes except integrase, and fusions and entry inhibitors	Yes except integrase, and fusions and entry inhibitors
Use of ARTs	83%	70%	29%	26%	37%
Evidence on the value of treatment	Clinical, Socio-economic	Clinical, Cost control; Quality of life	Clinical	Clinical; Socio-economic	Clinical, Cost control; Socio-economic; Quality of life

Source: CRA analysis

6

ROTAVIRUS DISEASE

Diarrhoea is a leading killer of young children worldwide, and rotavirus is the most common cause of severe diarrhoea.[257] Nearly every child is at risk of infection, with children six months to two years of age being the most vulnerable to infection, along with premature infants, the elderly, and those with weakened immune systems.[258]

If left untreated, it can lead to severe dehydration and death. Similarly, rotavirus diarrhoea is a common cause of clinic visits or hospitalisation among children in both industrialised and developing countries.[259] Therefore, medicines addressing rotavirus have the potential to reduce not only deaths but also hospital utilisation.

In this chapter we look the development of effective vaccines, before turning to the evidence regarding the value that rotavirus vaccination has delivered. We have focused on rotavirus disease within HICs (illustrated by Australia) and MICs (illustrated by Brazil). However, it is important to understand to different burden caused by rotavirus in these two countries.

In Australia, although rotavirus mortality among children younger than 5 years old was less than 10 in 2008, the virus was responsible for 28,502 hospitalisations of children aged under 5 between 2001 and 2010. The burden of rotavirus in Australia is summarised in Table 17.

Table 17: Summary of burden of disease in Australia

ROTAVIRUS RELATED BURDEN		YEAR
Total death under 5 years of age	<10	2008
Under 5 mortality rate (per 100,000)	0	2008
Rotavirus-coded gastroenteritis hospitalisations in children <5 years	28,502*	2001-2010
Rotavirus-coded gastroenteritis hospitalisation rates (per 100,000) in children <5 years	74.8**	2009-2010
Non-rotavirus coded gastroenteritis hospitalisations in children <5 years	1,207,978*	2001-2010
Non-rotavirus coded gastroenteritis hospitalisation rates (per 100,000) in children <5 years	875.6**	2009-2010

Source: CRA from different sources:[260] Note: *Total hospitalisations from 2001 to 2010; **Average rate across different patient ages

The starting situation was considerably different in Brazil. As illustrated in Table 18, a total of 857 children younger than 5 years old died in Brazil during 2008 as a

257 WHO, Unicef and the World Bank (2009), 'State of the world's vaccines and immunization', Third edition, November 2009.

258 PATH (2013), 'Rotavirus disease and vaccines: Frequently asked questions', April 2013.

259 WHO, Unicef and the World Bank (2009), 'State of the world's vaccines and immunization', Third edition, November 2009.

260 WHO (2012), '2008 rotavirus related death on children under 5 years', as of 31 January 2012; Dey et al (2012), 'Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program', the Medical Journal of Australia, 2012, 197, 8.

consequence of rotavirus; this represents a mortality rate of 5 children per 100,000. Looking at the burden that rotavirus has within the healthcare system, evidence suggests that in 2007, 1,176 hospitalisations were related to diarrhoeal episodes.

Table 18: Summary of burden of disease in Brazil

ROTAVIRUS RELATED BURDEN		YEAR
Total death under 5 years of age	857	2008
Under 5 mortality rate (per 100,000)	5	2008
Diarrhoeal consultations	604	2007
Diarrhoeal hospitalisations	1,176	2007

Source: CRA from different sources[261]

6.1. EVOLUTION OF ROTAVIRUS VACCINES

As illustrated in Figure 42, successful rotavirus vaccines have been recently developed.[262] In 2006, two new vaccines against Rotavirus A infection were shown to be safe and effective. RotaTeq, developed by Merck, was approved in 2006 while Rotarix, manufactured by GSK, was approved in 2008. [263]

Both rotavirus vaccines are oral live attenuated vaccines for use in infants, but there are differences in their composition and dosing. Rotarix is an attenuated human vaccine containing the G1P1[8] strain of rotavirus which is given in a two-dose course at 2 and 4 months of age, whereas RotaTeq is a human-bovine reassortant vaccine containing five strains (G1, G2, G3, G4, and P1[8]), which is given as three doses at 2, 4 and 6 months of age.[264,265]

According to news reports, new vaccines are being developed by manufacturers in India, China and Brazil. If successful, these could be available as soon as 2014 or 2015. The characteristics of these vaccines vary—some are live, attenuated vaccines, some are inactivated.[266]

261 WHO (2012), '2008 rotavirus related death on children under 5 years', as of 31 January 2012; Gurgel et al (2009), 'Incidence of rotavirus and all-cause diarrhea in northeast Brazil following the introduction of a national vaccination program', Gastroenterology, 137, 6.

262 The first rotavirus vaccine, RotaShield, developed by Wyeth, was licensed for use in the US in 1998. However, in 1999 the vaccine was withdrawn from the US market because of its association with intussusception. WHO, Unicef and the World Bank (2009), 'State of the world's vaccines and immunization', Third edition, November 2009.

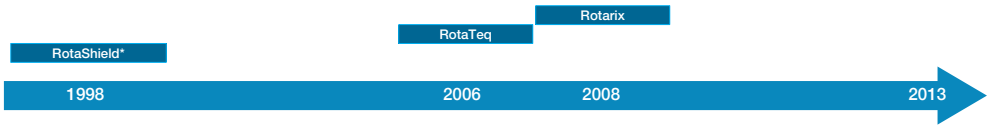
263 US Food and Drug Administration.

264 Kirkwood, et al (2011), 'Australian rotavirus surveillance program annual report, 2010/2011', Communicable disease intelligence, 35,4.

265 PATH, 'Two safe and effective rotavirus vaccines are saving lives today', available here http://sites.path.org/rotavirusvaccine/about-rotavirus/rotavirus-vaccines/

266 PATH, 'FAQ. Rotavirus disease and vaccines', available here http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/rotavirus-faq/#available

Figure 42: Anti-rotavirus vaccines available in the market, by FDA year of approval



Source: CRA analysis from difference sources; *RotaShield was removed from the market in 1999

WHO RECOMMENDATIONS FOR THE IMMUNISATION AGAINST ROTAVIRUS

Even though WHO recommended introduction of rotavirus vaccines into national immunisation programs of all countries worldwide in 2009, not all countries have included a rotavirus vaccine within their national immunisation programs." To "Even though WHO recommended introduction of rotavirus vaccines into national immunisation programs worldwide in 2009, not all countries have included a rotavirus vaccine within their national immunisation programs.

WHO Strategic Advisory Committee on Immunization recommends that the first dose of either Rotateq or Rotarix be administered during the period of 6 weeks to 15 weeks of age. WHO also recommends that sentinel surveillance for severe rotavirus gastroenteritis should be in place to monitor vaccine impact.[267]

6.2. ACCESS TO ROTAVIRUS VACCINATION

Even though WHO recommended introduction of rotavirus vaccines into national immunisation programs worldwide in 2009, not all countries have included a rotavirus vaccine within their national immunisation programs. Other countries, such as Canada, Thailand and Zambia have introduced rotavirus vaccines in pilot or regional programmes. Routine, public-sector use of rotavirus vaccines in low-income, Global Alliance for Vaccines and Immunisation(GAVI)-eligible countries is limited but expanding. Rotavirus vaccines are also available in more than 100 countries through the private market.[268]

Even among developed economies, few countries have chosen to include the rotavirus vaccine in the national immunisation plans. Among HICs, Australia was one of the first to nationally fund rotavirus vaccine. In Europe, for example, only Finland, Austria, Luxemburg and Belgium have included routine rotavirus vaccination of infants at the national level.[269]

Within MICs, Latin American countries have led the introduction of rotavirus vaccination within their immunisation programs. By January 2011, 14 of the 32 Latin American countries routinely offered rotavirus vaccines as part of their national

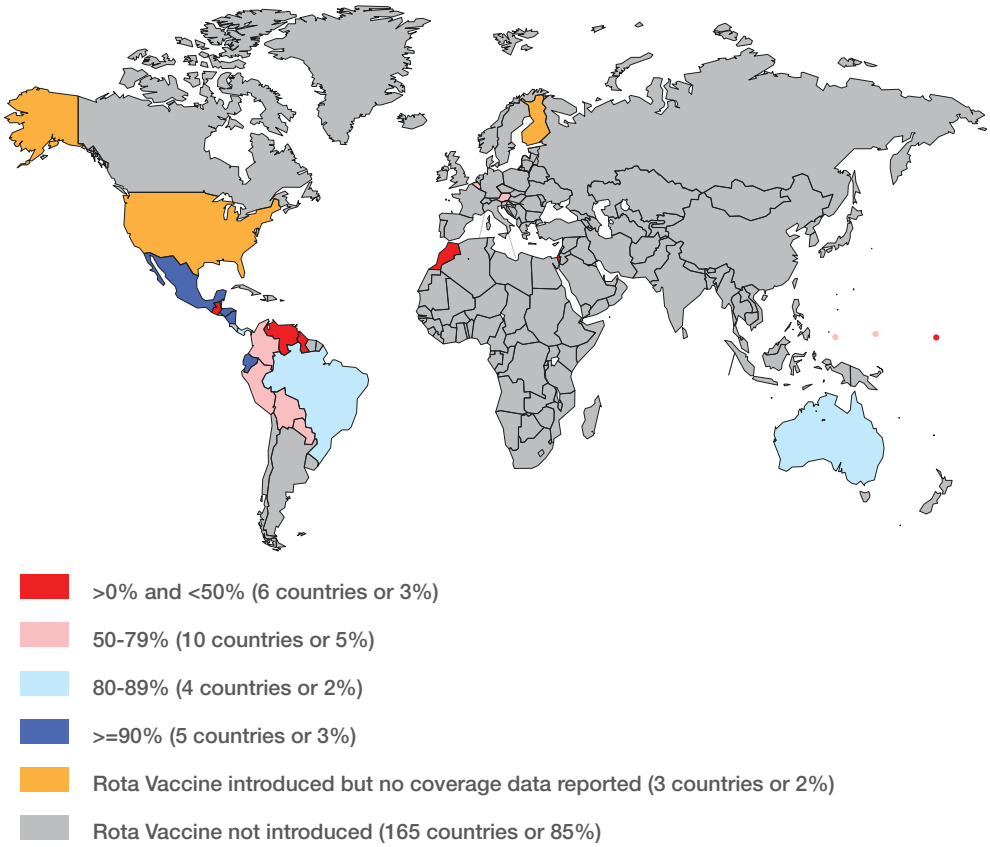
267 WHO (2011), 'New and under-utilized vaccines implementation NUVI. Rotavirus', available at http://www.who.int/nuvi/rotavirus/en/

268 PATH (2013), 'Rotavirus is the leading cause of death due to diarrhea in young children worldwide', available at http://sites.path.org/rotavirusvaccine/about-rotavirus/

269 ECDC (2013), 'Impact of rotavirus vaccination. Generix study proticol', European Centre for Disease Prevention and Control (ECDC).

immunisation schedule.[270] This is reflected in the immunisation coverage with rotavirus vaccines in infants, as Latin American countries showed to have the highest coverage levels across the globe (Figure 43).

Figure 43: Immunisation coverage with rotavirus vaccines in infants, 2010*



Source: WHO/UNICEF coverage estimates 1980-2010, July 2011; *Rotavirus vaccine coverage is the proportion of the surviving birth cohort that was administered the complete rotavirus vaccine series

ACCESS TO ROTAVIRUS VACCINATION IN AUSTRALIA

Australia was one of the first countries to introduce a nationally funded rotavirus vaccination program. Rotavirus vaccines were introduced into the National Immunisation Program (NIP) for all infants from July 1, 2007, with all state health departments making independent decisions on which vaccine to use.[271]

The Australian department of health provides data on immunisation coverage among the eligible population. Since the introduction of the program in 2007, more than 80% of Australian children younger than one receive the rotavirus vaccine. As Table 19 shows, in 2010 almost 85% of children younger than one year old received a complete rotavirus immunisation vaccination.

270 Desai, et al. (2011), 'Reduction in morbidity and mortality from childhood diarrhoeal disease after species A rotavirus vaccine introduction in Latin America – A Review', Memórias do Instituto Oswaldo Cruz, 106,8.

271 RotaTeq is administered in Victoria, South Australia, Western Australia (since May 2009) and Queensland, while Rotarix is in use in New South Wales, the Northern Territory, Tasmania and the Australian Capital Territory. Kirkwood, et al (2011), 'Australian rotavirus surveillance program annual report, 2010/2011', Communicable disease intelligence, 35,4.

Looking at the burden of disease data prior to the introduction of the vaccine, we can see that Australia decided to include the rotavirus vaccine within its national immunisation program to a) reduce the number of hospitalisations due to rotavirus in young children[272] and b) to reduce the burden within the indigenous population.[273]

Prior to the introduction of rotavirus vaccines in Australia, the best available estimates were that approximately 10,000 hospitalisations due to rotavirus occurred each year in children under 5 years of age,[274] equating to around half the hospitalisations for acute gastroenteritis in this age group[275] and affecting 3.8% of all children (1 in 27) by the age of 5 years. In addition to hospitalisations, an estimated 115,000 children under 5 years of age visited a GP, and 22,000 children required an emergency department visit due to rotavirus. [276]

Table 19: Percentage of children immunised against rotavirus at 12 months of age, Australia, 2007-2010

	2 OR 3 DOSES AT 12 MONTHS OF AGE
2007	83.8%
2008	82.3%
2009	84.8%
2010	84.7%

Source: Department of Health and Ageing, Immunisation coverage annual reports, 2007-2010

ACCESS TO ROTAVIRUS VACCINATION IN BRAZIL

In 2006, the Brazilian Ministry of Health introduced the single strain rotavirus vaccine, Rotarix, simultaneously in all 27 states through its national immunisation program in order to reach more quickly the fourth Millennium Development Goal of reduced child mortality. Under the national program, the federal government purchases vaccines, which are distributed to state and local immunisation programs and provided at no cost at public health facilities throughout the country.[277,278]

272 Additionally, an estimated 115 000 children <5 years of age visited a GP, and 22,000 children required an emergency department visit due to rotavirus. On the other hand, on average, there is only one death recorded as being due to rotavirus each year in Australia. NCIRS (2009), 'Rotavirus. Rotavirus vaccines for Australian children: Information for immunisation providers'.

273 Indigenous Australian infants and children are hospitalised with rotavirus gastroenteritis about three to five times more commonly than their non-Indigenous peers. NCIRS (2009), 'Rotavirus. Rotavirus vaccines for Australian children: Information for immunisation providers'.

274 Galati JC, Harsley S, Richmond P, Carlin JB. 'The burden of rotavirus-related illness among young children on the Australian health care system'. Australian and New Zealand Journal of Public Health 2006;30:416-21

275 Newall AT, MacIntyre R, Wang H, Hull B, Macartney K. 'Burden of severe rotavirus disease in Australia'. Journal of Paediatrics and Child Health 2006;42:521-7.

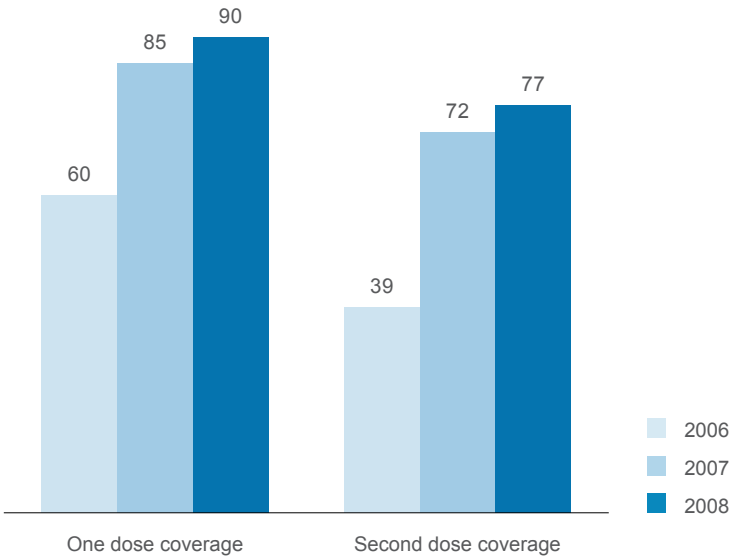
276 Carlin JB, Chondros P, Masendycz P, et al. 'Rotavirus infection and rates of hospitalisation for acute gastroenteritis in young children in Australia, 1993–1996'. Medical Journal of Australia 1998;169:252-6.

277 do Carmo, et al. (2011), 'Decline in Diarrhea Mortality and Admissions after Routine Childhood Rotavirus Immunization in Brazil: A Time-Series Analysis' PLoS Medicine, 8(4).

278 Rotavirus vaccination is recommended at 2 and 4 months of age. The first dose can be administered at 6–14 weeks, and the second dose at 14–24 weeks of age. do Carmo, et al. (2011), 'Decline in Diarrhea Mortality and Admissions after Routine Childhood Rotavirus Immunization in Brazil: A Time-Series Analysis' PLoS Medicine, 8(4).

Evidence shows that rotavirus vaccines are given to the majority of the Brazilian newborn population. As Figure 44 shows, coverage of two doses of human rotavirus vaccine was 39% in 2006 increasing to 77% after two years of the implemented national program. Although vaccine coverage varied by region, all regions achieved over 80% of vaccine coverage for the first dose in 2008.[279]

Figure 44: Vaccine coverage in Brazil, as % of the eligible population, 2006-2008



Source: Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International Journal of Infectious Diseases, 15

Hence, Australia and Brazil introduced a rotavirus vaccine within their NIPs around the same time. Although Australia and Brazil represent completely different healthcare systems, rotavirus vaccine coverage reached similar levels only two years after their introduction into the national programs.

6.3. THE VALUE OF ROTAVIRUS VACCINATIONS

The introduction of rotavirus vaccination within national immunisation programs has been shown to bring benefits to society from different perspectives. In this section we provide an overview of the benefits brought in Australia, and we then see if the same effects have been found in Brazil.

THE BENEFITS OF ROTAVIRUS VACCINATION ACHIEVED IN AUSTRALIA

Evidence suggests that the rotavirus vaccination program brings large benefits to the Australian economy and society. Given the low initial levels of mortality, it should be unsurprising that the majority of the observed benefits are those that arise from the reduction in hospitalisation costs.

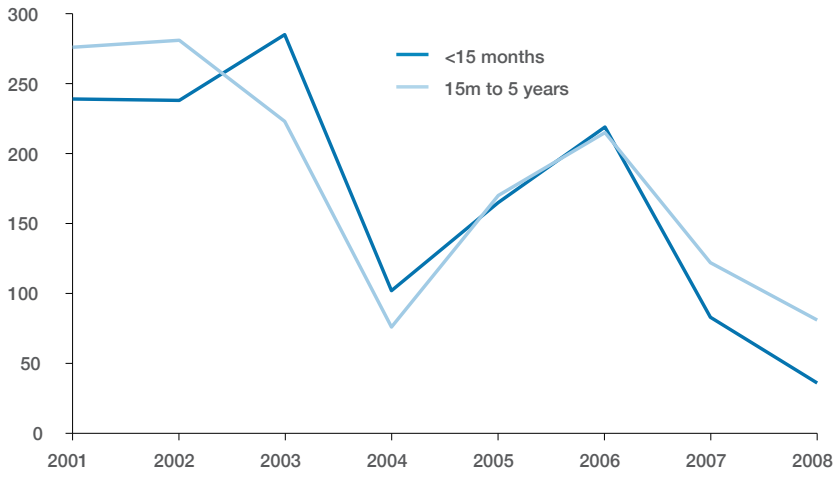
279 Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International journal of infectious diseases, 15.

Extensive clinical trials have shown both vaccines to be safe and highly effective in the prevention of severe diarrhoea due to rotavirus infections. Both rotavirus vaccines have been shown to have similar efficacy against rotavirus gastroenteritis (of any severity) of around 70%. The efficacy against severe rotavirus gastroenteritis is higher and ranged from 85% to 100% in clinical trials in many different countries.[280]

The majority of the studies assessing the effect of including rotavirus vaccination within the Australian immunisation program focus on the effects on hospitalisations, however, some evidence focuses specifically on the clinical benefits arising from the rotavirus vaccine. Indeed, Australian jurisdictions and paediatric hospitals have reported a decline in rotavirus disease on the basis of laboratory testing arising due to the program.[281]

In a study that examined weekly data from selected New South Wales laboratories between 2001 and 2008, the authors showed that rotavirus infection declined substantially both in children younger than 15 months and in older children (15 months to 5 years), as illustrated in Figure 45 below. [282,283]

Figure 45: Counts of laboratory rotavirus isolations by year and age from two Australian public pathology laboratories, 2001 to 2008



Source: Belshaw, et al (2009), 'Rotavirus vaccination one year on…', Communicable disease intelligence quarterly report, 33,3

Looking at the publicly funded rotavirus vaccination program in Queensland, another study found that rotavirus notifications declined by 53% (2007) and 65% (2008) among children younger than 2 years old. Additionally, the number of laboratory tests

280 Kirkwood, et al (2011), 'Australian rotavirus surveillance program annual report, 2010/2011', Communicable disease intelligence, 35,4.

281 Dey et al (2012), 'Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program', the Medical Journal of Australia, 2012, 197, 8.

282 Belshaw, et al (2009), 'Rotavirus vaccination one year on…', Communicable disease intelligence quarterly report, 33,3.

283 The authors also looked at gastroenteritis-related visits to the emergency department, which also experienced a substantial reduction since the introduction of the vaccine. The effects on healthcare utilisation are explored in the next section.

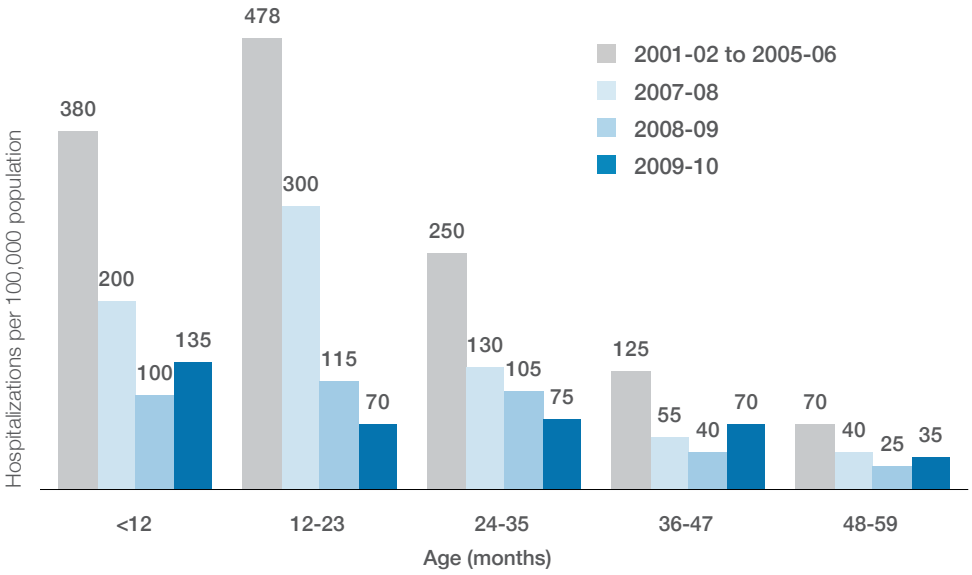
performed declined by 3% (2007) and 15% (2008), and the proportion of tests positive declined by 45% (2007) and 43% (2008) compared with data collected before introduction of the vaccination program.[284]

Controlling costs in the healthcare system

The introduction of rotavirus vaccines into the NIP in Australia has shown an early impact on the large disease burden of rotavirus, with significant declines in hospitalisation and emergency room visits reported since vaccine introduction.[285]

A recent study examining national data on all hospitalisations for severe acute gastroenteritis showed that a 71% decline in rotavirus-coded hospitalisations of children aged less than 5 years was registered, comparing periods before and after rotavirus vaccination. This represents the first study using national data from the Australian Institute of Health and the Welfare National Hospital Morbidity database between 2001 and 2010. As Figure 46 shows, rotavirus-coded hospitalisation rates have experienced a substantial reduction since the introduction of the rotavirus vaccine within the Australian immunisation program in 2007.[286]

Figure 46: Rotavirus-coded hospitalisation rates by age in children <5 years in Australia, 2001-2010



Source: Dey et al (2012), 'Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program', Medical Journal of Australia, 2012, 197, 8

Early evidence from the NIP in Australia also demonstrated that the introduction of both vaccines has been associated with a marked reduction in gastroenteritis admissions, supportive of both direct vaccine protection and indirect herd protection. Hospital admissions for both rotavirus gastroenteritis and non-rotavirus-coded

284 Lambert, et al (2010), 'Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland', the Medical Journal of Australia, 191,3.

285 Kirkwood, et al (2011), 'Australian rotavirus surveillance program annual report, 2010/2011', Communicable Diseases Intelligence, 35,4.

286 Dey et al (2012), 'Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program', the Medical Journal of Australia, 2012, 197, 8.

gastroenteritis were reduced following vaccine introduction in all states, not only for the age group eligible for NIP rotavirus vaccination, but also for children born priorly.[287] Marked reductions in acute gastroenteritis emergency presentations and short-stay unit admissions have also been observed.[288]

Similar result is reports local studies focused on particular paediatric hospitals. They have reported a decline in rotavirus disease in terms of the number of hospitalisations arising from the program: [289]

- A study that examined data on hospital admissions before and after the introduction of the rotavirus vaccination in South Australian children found an 83% reduction in hospital admissions for serious rotavirus gastroenteritis and a 48% on all-cause gastroenteritis in children aged less than six years.[290]

- Hospital admissions data was analysed for the hospitals in Queensland, Australia, between 2000 and 2008. The authors found an immediate reduction in rotavirus hospital admissions for individuals who were younger than 20 years after vaccine introduction in July 2007, a finding sustained in 2008. Hospitalisation rates for rotavirus and non-rotavirus acute gastroenteritis in all age groups before and after RV5 introduction were compared.[291]

- Similar results were found looking at The Children's Hospital in Sydney. Annual hospitalisations for rotavirus were collected from 2001 until 2.5 years following the introduction of rotavirus vaccines to the National Immunisation Program. Hospitalisations for rotavirus gastroenteritis declined in the two full rotavirus seasons (2008 and 2009) after vaccine introduction by 75% compared with mean annual hospitalisations from 2001 to 2006. The greatest decline was seen in those <12 months of age (93%), but the reduction occurred consistently across all age groups, even in children not eligible for immunisation, suggesting an effect on herd immunity.[292]

Although a large number of studies quantified the reduction on rotavirus-related hospital visits after the introduction of the vaccination program, none of them assessed the economic savings that these reductions represented for the Australian healthcare expenditure.

287 This was based on admission and rotavirus identification data from the major paediatric hospitals in three states together with state-based hospitalisation and vaccination data from Queensland, which were analysed for the years before, and up to 30 months following, rotavirus vaccine introduction. At that stage, rotavirus vaccine coverage in Australia was high, with 87% of infants receiving at least one dose.

288 Buttery et al (2011), 'Reduction in rotavirus-associate acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule', Paediatric Journal of Infectious Diseases, 30,1.

289 Dey et al (2012), 'Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program', the Medical Journal of Australia, 2012, 197, 8.

290 Clarke et al (2011), 'Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisation sin South Australian children following the introduction of rotavirus vaccination', Vaccine, 24, 29.

291 Field et al (2010), 'Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalisations in Australia', Pediatrics, 126.

292 Macartney et al (2011), 'Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme', Journal of Paediatrics and Child Health, 47,5.

Wider benefits to society

There is evidence that rotavirus vaccines have positive effects not only from a clinical and cost savings element but also from a wider perspective. A study looking at the implementation of a universal rotavirus vaccine program in Australia showed that rotavirus vaccination with both vaccines (Rotarix and RotaTeq) is a cost-effective health intervention in Australia from both a healthcare and a societal perspective. Overall, the authors found that Rotarix would cost AUS$60,073/QALY gained and RotaTeq AUS$67,681/QALY gained.

THE BENEFITS OF ROTAVIRUS VACCINATION ACHIEVED IN BRAZIL

The next question is whether there is evidence that the rotavirus vaccination program brought the same types of benefit to the Brazilian economy and society.

Therapeutic/Clinical benefits

Rotavirus vaccinations have been shown to bring significant therapeutic and clinical benefits to the Brazilian populations. In order to assess the effect of the NIP, several authors have developed national studies comparing diarrhoea-mortality among children younger than 5 years of age before and after the introduction of the program:

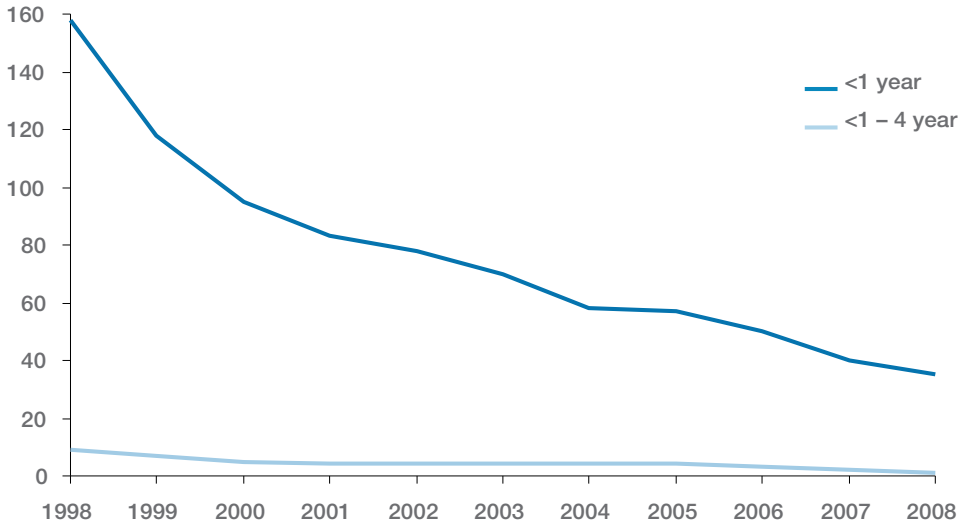
- One study looked at monthly national data on diarrhoea-related deaths among Brazilian children younger than 5 years old during pre-vaccine years (2002-2005) and post introduction of the rotavirus vaccination (2007-2009). They found a reduction of 22% of diarrhoea-mortality after the introduction of the vaccine.[293]

- Using data from the NIP and the Mortality Information System, vaccine coverage and mortality rates related to gastroenteritis in children younger than 5 years old were estimated. The authors found that during 2004-2005, the gastroenteritis mortality rate in children less than 1 year of age was 56.9 per 100,000, decreasing by 30% in 2007 and by 39% in 2008. In children between 1 and 4 years of age, the mortality rate was 4.5 per 100,000 during 2004-2005, decreasing by 29% in 2007 and by 33% in 2008. Figure 47 shows these results.[294]

293 do Carmo, et al. (2011), 'Decline in Diarrhea Mortality and Admissions after Routine Childhood Rotavirus Immunization in Brazil: A Time-Series Analysis', PLoS Medicine, 8(4).

294 Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International Journal of Infectious Diseases, 15.

Figure 47: Trends over time of gastroenteritis-related deaths by age group, Brazil, 1998-2008



Source: Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International Journal of Infectious Diseases, 15

The level of rotavirus-A detection within children less than 2 years old has decreased since the introduction of the immunisation program. A study based on 6,109 faecal samples across 18 Brazilian states among children less than 2 years old between 2005 and 2009 showed that the rates of rotavirus-A detection decreased from 33.8% in 2005 to 18.3% in 2009.[295]

Previous clinical studies provide evidence that rotavirus vaccines work effectively within the Brazilian population.

- The effectiveness of two doses of Rotarix was showed to be 77% effective among children aged 6 to 11 months using both rotavirus-negative control participants and control participants with acute respiratory tract infection. This clinical study used 70 rotavirus-positive case patients with severe diarrhoea, 484 rotavirus-negative control participants with diarrhoea, and 416 control patients with acute respiratory tract infection.[296]

- In clinical trials using children from Latin American, the single strain human rotavirus vaccine Rotarix showed a protective efficacy of 85% against severe rotavirus diseases.[297]

Controlling costs in the healthcare system

As with the clinical benefits, several authors have looked at the benefits that the rotavirus vaccination program brought to Brazil in terms of the reduction of diarrhoea-related

295 Anibal et al (2011), 'Laboratory-based rotavirus surveillance during the introduction of a vaccination program, Brazil, 2005-2009', The Pediatric Infectious Disease Journal, 30, 1.

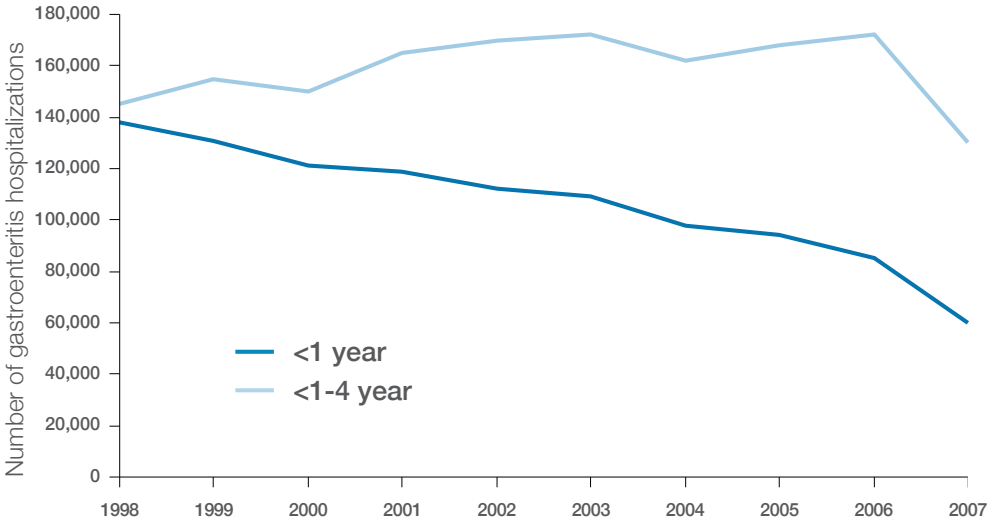
296 Correira et al (2010), 'Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil', The Journal of Infectious Diseases, 201:363-9.

297 Linhares et al (2008), 'Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study', The Lancet, 371: 1181–1189; Ruiz-Palacios et al. (2006), 'Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis', New England Journal of Medicine, 354: 11–22.

hospitalisation rates. Indeed, hospital-based surveillance for rotavirus-associated gastroenteritis among children younger than 5 years of age is an important tool to evaluate the impact of vaccination on the burden of severe rotavirus disease. [298]

Although an economic quantification of the savings has not yet been developed, the papers provide enough evidence to prove that rotavirus vaccinations lead to reductions on hospital usage. This is illustrated in Figure 48.

Figure 48: Trends in hospitalisations from all-cause gastroenteritis in children younger than 1 and 1 to 4 years, Brazil, 1998-2007



Source: Lanzieri et al (2011), 'Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil', International Journal of Infectious Diseases, 15

And supported in a number of other analyses:

- do Carmo et al (2011) compared the diarrhoea-related hospitalisation rates among Brazilian children. They found that among children younger than 5 years old, 17% fewer admissions were observed after 2006, when the routine immunisation began.[299]Another study highlighted that since vaccines were introduced in 2006, there has been an overall reduction in diarrhoeal consultations, from 3,020 in 2004 to 604 in 2007; reductions were greatest among children under 5 years old. Diarrhoeal hospitalisations decreased from 2,121 in 2003 to 1,176 in 2007.[300]

- A study focusing on a hospital in Sao Paolo assessed the impact of the immunisation program on the incidence of severe rotavirus acute gastroenteritis (AGE).[301] They collected data from January 2004 to December 2008 and followed up with the children younger than 5 years old who received the vaccine. The authors found a 29%

298 Safadi et al (2010), 'Hospital-based surveillance to evaluate the impact of rotavirus vaccination in Sao Paulo, Brazil', The Pediatric Infectious Disease Journal, 29, 1019-1022.

299 do Carmo, et al. (2011), 'Decline in Diarrhea Mortality and Admissions after Routine Childhood Rotavirus Immunization in Brazil: A Time-Series Analysis' PLoS Medicine, 8(4).

300 Gurgel et al (2009), 'Incidence of rotavirus and all-cause diarrhea in northeast Brazil following the introduction of a national vaccination program', Gastroenterology, 137, 6.

301 AGE was defined as diarrhoea (three or more loose, or looser-than-normal, stools in a 24-hour period), over a 14 day duration.

reduction in the number of hospitalisations of all-cause AGE and a 59% reduction in the number of hospitalisations of rotavirus AGE among children younger than 5 years in the post-vaccine period compared with the pre-vaccine period. [302]

Clinical studies developed before the program was implemented showed the ability of the rotavirus vaccine to reduce hospitalisation events:

Correira et al (2010) found that the vaccine was highly effective against rotavirus disease: hospitalisation of children 6 to 11 months of age was 85% lower among those who received the vaccine than it was among the rotavirus-negative control participants, and 83% lower than among those with acute respiratory tract infection. [303]

Wider benefits to society

Not many papers, when assessing the impact of the vaccination program, include the value of the life gained by the children receiving rotavirus vaccination.[304] However, several studies that assessed the cost-effectiveness analysis of introducing routine rotavirus vaccinations in Brazil included both clinical and non-clinical benefits.

De Soarez et al (2008) conducted a simulation analysis before the introduction of the NIP. The analysis considered a hypothetical cohort of approximately 3,300,000 newborns followed over 5 years. They used different probabilities on diarrhoea incidence rates, proportion of severe cases, vaccine coverage and price from published papers to develop their estimates. They found that universal rotavirus vaccination was a cost-effective strategy for the Brazilian government as the cost per DALY is less than one time the GDP per capita.[305]

- The vaccination programme was estimated to prevent 54% of the cases of rotavirus gastroenteritis and 75% of the rotavirus-associated deaths.
- Costing 18.6 Brazilian reals (R$) per dose of vaccine, the program would cost R$ 121,673,966.
- The indirect cost savings that could be achieved in the public healthcare system would reach R$ 38,536,514.
- Brazil would also save R$ 71,778,377 on direct and indirect costs to the society.
- The program was estimated to cost R$1,028 and R$1,713 per life-years saved (LYS) from the societal and healthcare system perspectives, respectively.

The results are presented in Table 20 below.

302 Safadi et al (2010), 'Hospital-based surveillance to evaluate the impact of rotavirus vaccination in Sao Paulo, Brazil', The Pediatric Infectious Disease Journal, 29, 1019-1022.

303 Correira et al (2010), 'Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil', The Journal of Infectious Diseases, 201:363-9.

304 De Soarez et al (2008), 'Cost-effective analysis of routine rotavirus vaccination in Brazil', Pan American Journal of Public Health, 23, 4.

305 This follows WHO cost-effectiveness definition.

Table 20: Cost-effectiveness of rotavirus vaccination in Brazil, 2004

INCREMENTAL COST-EFFECTIVENESS RATIO	SOCIETAL PERSPECTIVE (R$)	HEALTHCARE SYSTEM PERSPECTIVE (R$)
Cost per case averted	29	48
Cost per death averted	70,955	118,228
Cost per life-years saved	1,028	1,713

Source: De Soarez et al (2008), 'Cost-effective analysis of routine rotavirus vaccination in Brazil', Pan American Journal of Public Health, 23, 4

Similar results were found by Consentla et al (2008). The authors also developed a simulation analysis using a hypothetical annual birth-cohort followed for a five-year period. The main outcome measures included in the analysis were the reduction in disease burden, lives saved, and disability-adjusted life-years (DALYs) averted. They found that the vaccination program would save the life of 1,804 children and 60,694 DALYs.[306]

6.4. THE VALUE OF A ROTAVIRUS VACCINE IN HICS AND MICS

Diarrhoea is a leading killer of young children worldwide, and rotavirus is the most common cause of severe diarrhoea. Rotavirus diarrhoea is a common cause of clinic visits or hospitalisation among children in both industrialised and developing countries. If left untreated, it can lead to severe dehydration and death.

Two vaccines against rotavirus A were launched in 2006 and 2008. In order to prevent children being infected by rotavirus. A number of countries have included a rotavirus vaccine in their NIP. We focused the analysis on a HIC and a MIC that nationally provide rotavirus vaccination, choosing Australia and Brazil as they included rotavirus vaccines in their national programs around 2007, and two years later almost 80% of their young children were covered by the vaccine.

Rotavirus vaccination programs have been shown to bring a wide range of benefits within both HICs and MICs, as illustrated in Table 21. In Australia the biggest benefit we observed was related to the reduction in hospitalisation costs, while in Brazil we observed clinical and therapeutic benefits as well as those related to hospitalisation costs. These results reflect the fact that rotavirus-related mortality is almost non-existent within HICs while is still significant within MICs.

306 Constenla, et al (2008), 'Economic impact of a rotavirus vaccine in Brazil', Journal of Health, Population and Nutrition, 26,4.

Table 21: The value of rotavirus vaccines: Australia vs. Brazil

	AUSTRALIA	BRAZIL
Therapeutic/clinical value	✓	✓ (including a significant impact on mortality)
Controlling costs	✓	✓
Wider benefits	✓	✓

Source: CRA analysis

Rotavirus therefore provides a case study where both HICs and MICs clearly benefit from the introduction of an innovative medicine but where MICs are likely to receive a wider variety of benefits than HICs.

7

POLICY IMPLICATIONS

In the previous chapters, we have set out the evidence regarding the value that innovative treatments have delivered in MICs. This varies depending on the therapy area. Rotavirus and HIV/AIDS have the clearest evidence that innovative treatments have benefited patients, the healthcare system and the society in MICs. For other therapy areas, such as CHD, diabetes or depression, the evidence is relatively more limited. There is evidence of clinical benefits, but even here, there is still considerable room for further value to be realised as policymakers place a higher priority on NCDs. The evidence shows that benefits could be significant if treatment was more widely used. These findings are summarised in Table 22.

Table 22: Value achieved through innovative treatments within MICs

	CLINICAL BENEFITS	HEALTHCARE BENEFITS	SOCIETAL BENEFITS	EVIDENCE OF OVERALL BENEFITS ACHIEVED
CHD	✓	✓		Medium
Depression	✓			Limited
Rotavirus	✓	✓	✓	Compelling
Diabetes	✓*	✓		Medium
HIV/AIDS	✓	✓	✓	Compelling

Source: CRA analysis; Ticks added if the dimension of value if observed within MICs. Note: *mixed results were found for China

In this chapter, we draw on the evidence from the case studies to draw five policy implications.

7.1. THE ESTABLISHMENT OF A POLICY PRIORITY

If we consider the countries and therapy areas where there is the clearest evidence of value being delivered in MICs, this typically occurs once this has been recognised as a priority area at the national level. HIV/AIDS and, to a less extent, rotavirus have been identified as priority for governments in the case study countries. This has clearly meant that resources were assigned to ensure access to treatment. In both of these areas, clinical benefits, healthcare savings and societal benefits have been achieved since the introduction of innovative treatments.

HIV/AIDS has been of great concern within MICs, leading governments around the globe to implement specific national strategies. These were aimed at controlling the HIV/AIDS epidemic by preventing transmission and providing access to treatment. As explained above, all the case study countries offer ART coverage through their national plans to any affected citizens and the access to medicines is highly related to the recognition of HIV as a priority.

Rotavirus, although less high profile, has also been seen as a public health priority. In Brazil, the federal government purchases rotavirus vaccines, which are then distributed to the state and local immunisation programs and provided at no cost within public health facilities. Evidence shows that two years after the introduction of the rotavirus vaccination, the coverage of the vaccine across Brazilian children younger than 12 months was 77%.

For NCDs, political prioritisation also appears important, particularly, where the main limitations that are preventing the benefits of innovative treatments from being brought to MICs are the healthcare infrastructure and cultural barriers. Only in recent years, have we seen CHD, depression, diabetes being given significant attention. This appears especially important where there are cultural obstacles. As highlighted in Chapter 3 this is particularly true for mental illnesses, to which a stigma is still attached within MICs (and in many HICs). This means that patients suffering from depression are not getting treatment for fear of stigmatisation. Where MICs, as illustrated by Chile, adopt similar programs to those used in HICs, this can have significant consequences. Indeed, the national depression initiative in Australia, 'beyondblue', was able to change attitudes regarding the mental illness. Similarly, a program applied in Japan was able to lower suicide rates in participating prefectures. Emulating such HIC awareness programs may remove barriers to depression treatment in MICs.

There appears considerable unexploited value in some of the therapy areas. This is especially relevant for CHD, for which governments have already started to define and even implement national policies. It is not surprising that when a government has recognised the burden of a disease and has identified the particular needs of the society, greater benefits have been achieved. However, it is also clear that in some MICs there have been "false dawns" where national programmes have been announced but where ultimately they have not resulted in patients receiving the value of innovative medicines. Establishing the therapy area as a policy priority is clearly only a necessary but not sufficient condition for this to occur.

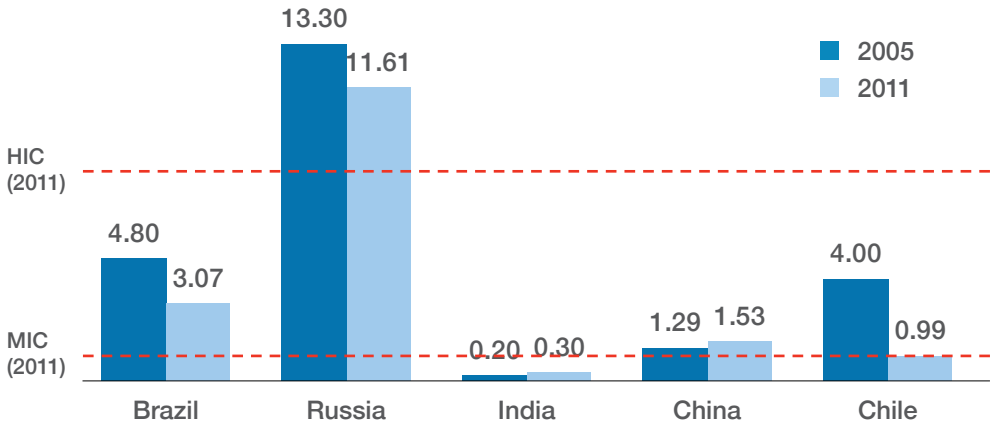
Policy implication: Ensuring that the widest population receives the value of innovative medicines often requires a national programme to increase awareness and overcome cultural challenges

7.2. THE LEVEL OF INFRASTRUCTURE REQUIRED TO ADOPT INNOVATION

It is also clear that access to innovative medicines also depends on the associated healthcare infrastructure. Without patients being identified, diagnosed, tested and appropriately managed it is not possible to increase access and, unsurprisingly, we are then unlikely to observe benefits from innovative medicines in MICs.

For CHD, diabetes or depression, for example, the main barrier to treatment is that patients suffering or at risk of suffering from these diseases are not always diagnosed. Normally the availability of specialist doctors per patient population is significantly smaller in MICs than in HICs. As illustrated in Figure 49.

Figure 49: Number of psychiatrists per 100,000 population



Source: WHO Mental Health Country Profiles, 2005 and 2011; WHO (2011), 'Mental Health Atlas 2011'.

In addition, some diagnosis protocols require advanced equipment that is only available in larger cities and for a particular set of patients. Therefore, even if the treatment are relatively inexpensive, as are drugs for CHDs or depression, patients are not able to get access, as their illness is not recognised.

The largest benefits have been achieved in those therapy areas where the infrastructure required to introduce innovation is smaller or where it has been seen as a priority (and a significant investment in infrastructure has followed). The extreme example remains in rotavirus vaccination, for which the only infrastructure required is ensuring that all newborn babies receive the vaccine.

In contrast, CHD, diabetes and depression, are therapy areas that require availability of specialists or sophisticated technology. Indeed, as not all the population has access to specialists who are able to define and monitor the treatment, the achievement of benefits within these therapy areas is limited. This is particularly relevant to depression, which requires a combination of pharmacological and psychological treatment.

This implies that value of innovative medicines, especially for NCDs, requires integrated policies in developing infrastructure to diagnose and manage patients, as well as access to innovative medicines. This has been successfully applied in MICs for some therapy areas. Looking at the HIV/AIDS plans applied, we found that in all the case-study countries the programs included different types of actions. In Botswana, for example, where ARTs are provided across the population, most of the government resources are designated to support AIDS prevention, care and treatment. The plan was successfully implemented and has brought benefits from different perspectives. Botswana not only has received the most therapeutic/clinical value from ARTs among study countries, but also has experienced reduction of absenteeism linked to HIV/AIDS since implementing the program.

Policy implications: For medicines to deliver value, there needs to be appropriate healthcare infrastructure, this works best when integrated programmes are used to ensure diagnosis, testing, access to medicines and maintenance of patients on a course of treatment

7.3. VALUE IS DELIVERED THROUGH BOTH RADICAL OR INCREMENTAL INNOVATION

The benefits from innovative treatments have been delivered through different types of innovation. We find that whether the innovation is perceived as radical or incremental is not associated with the value achieved.

Most would characterise rotavirus and HIV/AIDS as involving radical innovation. However, it is clear that the development of classes of medicines for HIV, fixed dose combinations and targeting the medicines on new patients groups has brought significant value to patients and society more generally.

Another example can be found in the types of innovation within the CHD therapy area, where new treatments have been developed both by creating new classes of medicines and by creating new molecules within a class. Often the first in class medicine, although representing a radical innovation, has greater side effects than the products that subsequently are launched onto the market. This is clearly the case for the depression case study, where later entrants reduced the likelihood of side-effects and tolerability for depression. This is also the case for new classes of medicines for CHD. Although the benefits achieved within MICs are still far from what could be reached, CHD is a good example of a therapy area where benefits can be delivered through both radical and incremental innovation.

Policy implications: The healthcare system needs to incorporate both incremental and radical innovation

7.4. THE VALUE OF PATENTED AND OFF-PATENT MEDICINES IN CASE STUDY THERAPY AREAS

Based on the case studies chosen for this project, we found that the current status of patent protection does not inhibit the value of the innovation to society. The study shows value to society being delivered by both patented and off-patent medicines. Indeed, in the therapy areas where treatments have brought the greatest value, rotavirus and HIV/AIDS, the medicines used are still protected through the IP system. In contrast, in therapy areas where the existing treatment has been on the market since the '80s and is now off-patent, and low-cost drugs are available – depression and CHD – only limited benefits have been realised and there is still significant value to be extracted.

Table 23: IP status and evidence of benefits

	EVIDENCE ON OVERALL BENEFITS ACHIEVED IN MICS	IP STATUS
CHD	Medium	Off-patent[1]
Depression	Limited	Off-patent[1]
Rotavirus	Compelling	Protected
Diabetes	Medium	Mixed
HIV/AIDS	Compelling	Protected[2]

Source: CRA analysis; Note: [1]although there are products that are still patented, the gold standard treatment is off-patent; [2]protected products may be available in MICs through voluntary licenses

Whether we can observe the value of different classes is not directly related its intellectual property protection and both patented and off-patent products can deliver value to MICs and HICs.

Policy implications: There is not a simple relationship between whether we can observe value and the current intellectual property protection of the medicines

7.5. A WIDE DEFINITION OF VALUE SHOULD BE RECOGNISED

As set out in the previous chapters, innovative medicines have delivered a broad range of benefits affecting not only patients but also the healthcare system and the society in general. We tested this directly by comparing the composition of benefits delivered in a MIC versus a HIC. Evidence shows that the full range of benefits can be achieved in both HICs and MICs and for some therapy areas a wider variety of benefits is achieved in MICs than HICs.

The rotavirus vaccination provides a good example of a therapy area for which innovation has brought value to patients but also wider benefits. After the introduction of the rotavirus vaccine into the immunisation programs of both Australia and Brazil, not only was there a reduction of child mortality rates due to gastrointestinal diseases but also a reduction of healthcare-related costs was achieved. In addition, the hospitalisation rates related to gastrointestinal diseases were significantly reduced in both Australia and Brazil.

We reach a similar conclusion for NCDs. For example in the diabetes case study, treating diabetes diseases has brought a wide range of benefits within HICs. As diabetes drugs have reduced diabetes-related mortality rates within HICs, they have helped to reduce direct healthcare costs associated with the disease and have also been shown to bring wider benefits to the society. The same is true in China, although the composition of these benefits is likely to be different.

Looking at the other case studies, we also found evidence of value being delivered through reduced healthcare costs (CHD, diabetes) and through benefits to the wider economy (HIV).

There is considerable scope over the long term for MIC health authorities to refine their approaches to assessing the value of modern medicines from a national perspective. We would recommend therefore that a modest investment of central resources in building better epidemiological and cost databases to support the development of modern methods of evaluating the relative value of alternative therapies.

Policy implications: In MICs, as in HICs, value can be delivered directly to patients, in terms of cost savings to the healthcare system and to wider society, this needs to be reflected in how medicines are assessed

7.6. CONCLUSIONS

The purpose of this paper was to set out the evidence that innovative medicines deliver value in MICs and to compare this to evidence from HICs. In all of the therapy areas considered these is evidence of value delivered but it is clear that the quality of the available evidence is weaker than in HICs.

The extent of access to medicines is a significant factor in the value they deliver. The cost of medicines has an impact on how widely they are used, but we have found that the value delivered within innovative treatment across MICs depends on several other elements, particularly whether governments have chosen to prioritise that therapy area, and the availability of the appropriate infrastructure to implement the innovation.

It is clearly the case that innovative medicines deliver value to patients but also through a reduction in healthcare costs and to wider society. Although the categories are often the same, the composition of this does vary in MICs compared to HICs. In some cases, medicines offer greater benefits in MICs and in some cases less.

We have found that value can be delivered through radical innovation, offering a treatment where none previously existed and through incremental innovation, reducing side effects, expanding choice of treatments or widening the patient population. Both forms of innovation bring value to MICs, just as it does in HICs. Historically, the speed of access to some of these classes has been considerably slower than in HICs. However, medicines for rotavirus and HIV and some of the more recent innovations in CHD and diabetes show speed of access is increasing. This suggests that several conditions are required for value to be delivered to MICs but the significance of IP status of the class is sometimes over-emphasised. A description of the case studies related to the level of value achieved is presented in Table 24.

Table 24: Summary table

	EVIDENCE ON OVERALL BENEFITS ACHIEVED IN MICS	EFFECTIVE CLASSES OF TREATMENT	GOVERNMENT PRIORITY	INFRASTRUCTURE REQUIRED	TYPE OF INNOVATION
CHD	Medium	Significant impact across range of conditions	Recent	Medium	Radical & Incremental
Depression	Limited	Effective for some patients but still significant unmet need	No	Large	Radical
Rotavirus	Compelling	Significant reduction in risk of mortality	Yes	Minimum	Radical
Diabetes	Medium	Transformed into a chronic conditions and avoided significant health issues	No	Medium	Incremental
HIV/AIDS	Compelling	Transformed to a chronic condition for many	Yes	Medium	Mixed

Source: CRA analysis

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CRA Charles River Associates

CRA International
99 Bishopsgate
London EC2M 3XD
United Kingdom

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