Expanding access to monoclonal antibody-based products

A global call to action

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Executive summary

Monoclonal antibodies are one of the most powerful tools in modern medicine. More than 100 of them have been licensed over the past 30 years and they are transforming the way doctors treat, prevent and even cure serious non-communicable diseases, including many cancers and autoimmune disorders. These monoclonal antibody products are significantly more effective than previously available therapies and are often better tolerated and easier to deliver. There's also a rapidly growing pipeline of monoclonal antibodies to treat and prevent many existing and emerging infectious and neglected diseases.

Millions of people around the world stand to benefit both from existing monoclonal antibody-based products and those in development. Rates of non-communicable diseases are on the rise in many developing countries. In addition, there are numerous existing and emerging infectious disease threats, including COVID-19, Ebola and HIV, for which monoclonal antibodies are poised to play an important role in treatment and prevention. As the COVID-19 pandemic has shown, no country is immune to the threat posed by emerging infectious diseases. If monoclonal antibodies prove to be effective for COVID-19, ensuring prompt, equitable and affordable global access to these products, as well as others, will be imperative.

But as this report details, global access to monoclonal antibody products is now severely limited in many countries. Today, the market for monoclonal antibodies is overwhelmingly in high-income countries. Few, if any, monoclonal antibodies are registered in low-income countries, and those that are registered in many middle-income countries are often unavailable in their public health systems, making them prohibitively expensive. This gap in access will only widen because monoclonal antibodies are an increasingly large proportion of pharmaceutical company pipelines.

99% of deaths from respiratory syncytial virus occur in low- and middle-income countries.

99% of the sales of Synagis, an antibody-based preventive, are in the US and Europe.

For global access to monoclonal antibodies to be a reality, these innovative products have to be both available and affordable.

Identifying pathways to provide affordable, timely and sustainable access to monoclonal antibody-based products across the globe is therefore a global health priority.

There is not a simple solution to this problem. Monoclonal antibodies are more complex and expensive to develop and produce than small molecule generic drugs. And the business and partnership models that have vastly expanded global access to some HIV drugs are not necessarily applicable or sufficient. Ensuring monoclonal antibodies are available and affordable globally will require new ways of thinking, new types of collaboration and new ways of doing business.

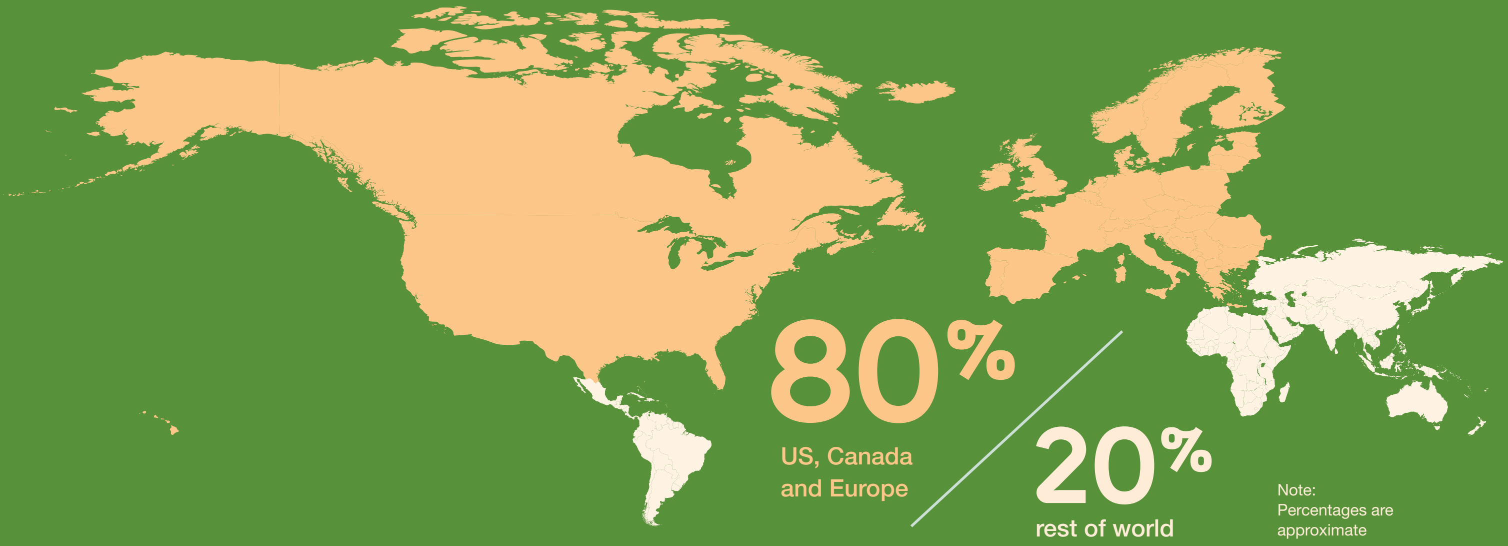
This report identifies a series of parallel actions that are required to expand access to monoclonal antibodies. The process starts with advocacy and awareness, but it also requires that regulatory and policy issues are addressed, and that technological advances are applied throughout the process of identifying, optimising, producing and delivering more potent, lower-cost monoclonal antibody products. New business models that promote the availability and affordability of these products are also necessary. Together, these actions will make it possible to address the growing inequity to these products, saving or improving millions of lives in the process.

Progress can't come soon enough. The goal of this report is to catalyse discussion, collaboration and action. Pharmaceutical companies, global health agencies, public sector entities, philanthropic organisations and ministries of health must join forces to make global access to transformative monoclonal antibody products a priority, and a reality.

The time to act is now.

Reshaping the monoclonal antibody world

Today's global market for monoclonal antibodies is highly unbalanced.



Ensuring equitable access requires four parallel yet vital commitments.

Increase awareness

Spread the word that monoclonal antibodies save lives

Expand availability

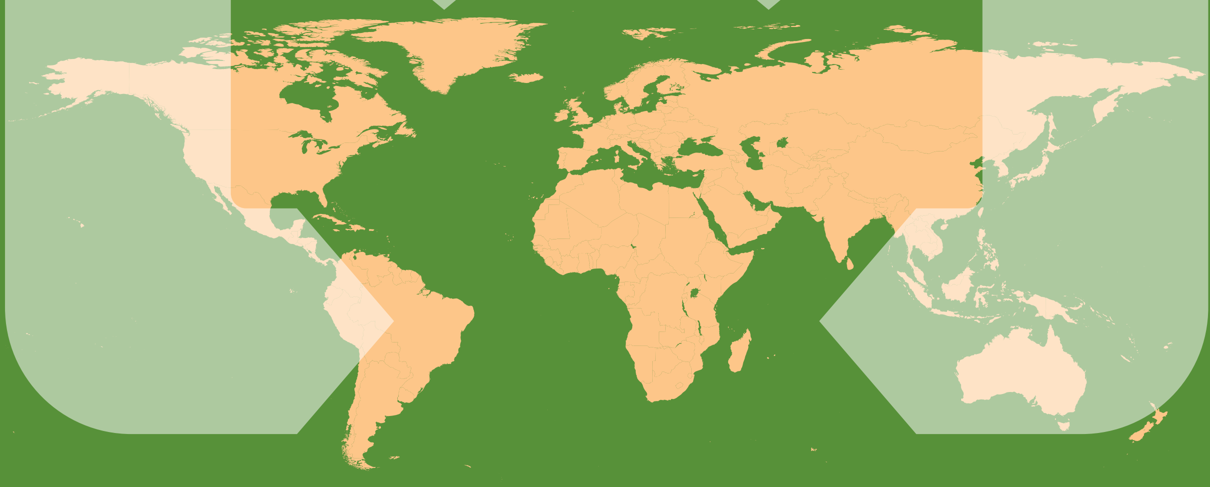
Support broader registration of antibody products across the globe

Apply innovations

Invest in and deploy new technologies to lower development costs

Create new models

Establish business models that enable different market approaches and promote access



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Methodology

Scope

The goal of this report is to assess the factors impeding access to mAbs in low- and middle-income countries, particularly within public health systems, and to formulate a series of recommendations for expanding global access to affordable antibody therapies. The classification of low-, middle- and high-income countries is based on World Bank classifications.

The report highlights opportunities for expanding access to monoclonal antibodies for cancers and autoimmune diseases, as well as those for neglected and viral/bacterial infectious diseases that are anticipated to represent a significant percentage of the future antibody market. These include antibodies against SARS-CoV-2, HIV, respiratory syncytial virus (RSV), rabies, Ebola, filoviruses, viral enteric pathogens and gram negative bacterial enteric pathogens, including *E.coli, Klebsiella p., Shigella* and *Salmonella*, which are on the World Health Organization's (WHO) and the US Centers for Disease Control and Prevention's lists of critical drug-resistant pathogens, as well as gram-positive bacterial enteric pathogens such as *C. difficile.*

Approach, data collection and analyses were based on two methods. A robust assessment was conducted of peer-reviewed biomedical literature, news sources, organisational websites, drug labels, recognised global and national datasets (including those available from the Institute for Health Metrics and Evaluation), the WHO, clinical trial registries, national regulatory agencies, national patent offices, drug pricing databases and market reports to capture the current state of the innovative and biosimilar mAb markets. Reports on antibody pricing models, with a focus on access to antibodies in public health systems in LMICs were analysed, and Charles River Associates (CRA) was commissioned to extract more detailed information on pricing pressures and models, with a focus on understanding global access challenges.

Additionally, a series of more than 100 interviews were conducted with global-health focused organisations, ministries of health, academic institutions, regulatory authorities, antibody-focused biosimilar/biotechnology companies and multinational pharmaceutical companies with large antibody pipelines. Focused stakeholder meetings were convened in India, where local participants and influencers were invited to discuss the challenges and opportunities for global access to antibodies. Smaller group discussions and individual stakeholder consultations were convened in sub-Saharan Africa (SSA) and in several high-income countries. The list of organisations consulted in this process is on page 2 of the Appendix to this report.

Several case studies were then selected of licensed monoclonal antibodies to illustrate the impact they have had on non-communicable, communicable and neglected diseases, and to evaluate the availability of the products and their impact in high-, middle- and low-income countries for which data are available. Case studies were selected because they cover a broad range of mAbs for non-communicable diseases (cancers and autoimmune diseases), communicable diseases (RSV and *C. diff* infections) and neglected diseases (rabies). The case studies cover antibodies that were approved more than 15 years ago (e.g. Herceptin®, the first targeted antibody for breast cancer; Humira® and Enbrel®, which are the gold standard treatments for rheumatoid arthritis; and Synagis®, the first licensed preventive antibody for an infectious disease); as well as other more recent approvals (e.g. Keytruda®, Rabishield®, Twinrab®, and Zinplava®). A landscape analyses of emerging, neglected and endemic infectious disease mAbs and more detailed examination of some pipeline monoclonal antibodies for infectious diseases, including COVID-19, HIV, Ebola, Nipah/Hendra and influenza, are included in supplemental sections of this report. Supplemental sections of this document cover the following topics: the emerging role of monoclonal antibodies in epidemic/pandemic preparedness and response; monoclonal antibodies: a new era in the treatment and prevention of disease; the development of HIV-specific broadly neutralising antibodies; combination monoclonal antibodies and alternate formats; and India's biopharmaceutical business: an evolving success story.

Monoclonal antibodies are transforming human health

Key findings:

Monoclonal antibodies (mAbs) are one of the most powerful tools in modern medicine.

An analysis of select licensed mAbs for both non-communicable and infectious diseases indicates that availability (including registration, inclusion on national medicine lists and reimbursement through public health systems) and affordability are two of the biggest barriers impeding global access.

Most licensed mAbs are for non-communicable diseases, including cancer and autoimmune diseases.

Only seven of more than 100 currently licensed mAbs are for infectious/neglected diseases; however, mAbs are poised to play a major role in treating and preventing infectious/neglected diseases that disproportionately impact developing countries, as well as emerging pathogens with the potential to spread globally.

mAbs are a large and growing segment of the pharmaceutical market and are the largest class of biologic products in development.

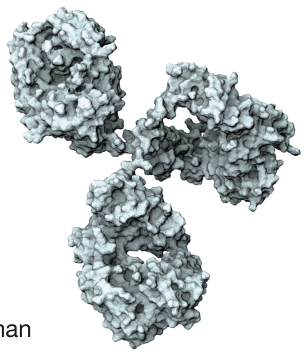
When and where lower-priced biosimilar mAbs are available, they can increase access, but not sufficiently.

Monoclonal antibodies are one of the most powerful tools in modern medicine. These proteins act specifically against their targets — anything from viruses and bacteria to cancerous cells — and can safely and effectively prevent or treat a growing number of diseases (Figure 1, next page), some of which were previously difficult, if not impossible, to treat. Millions of people have benefited from mAb-based therapies in the 30 years since the first one was licensed.

For more, see the supplement to this report: *Monoclonal antibodies: a new era in the treatment and prevention of disease*

The majority of licensed mAbs are used to treat non-communicable diseases, including cancers and autoimmune diseases. Today's successful cancer immunotherapies — including more than 40 licensed mAbs that directly or indirectly stimulate the immune system to attack and kill tumor cells — are revolutionising cancer treatment and have significantly improved overall and long-term survival

What are monoclonal antibodies?

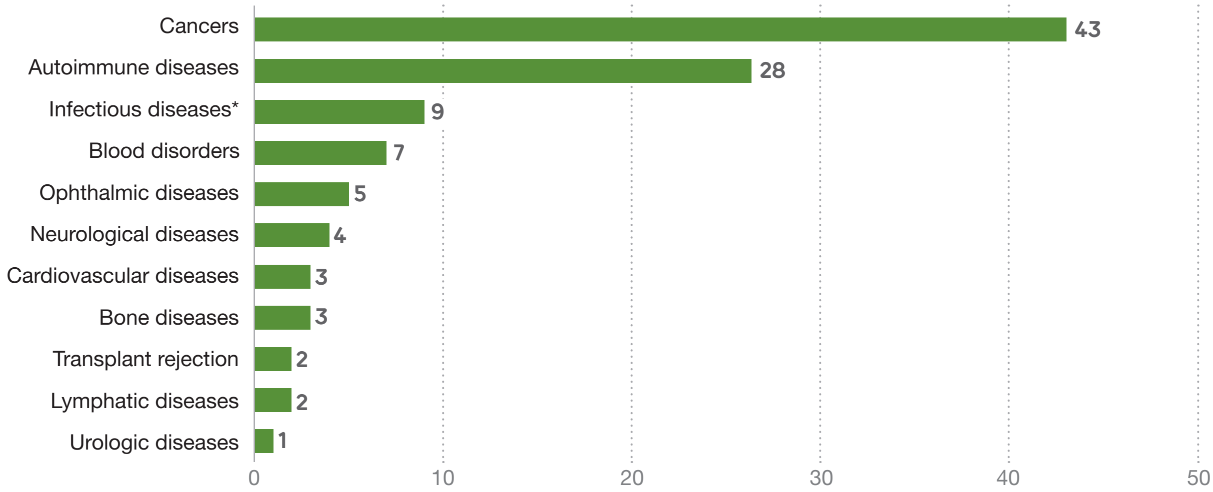


Antibodies are proteins generated by the immune system. They are one of the primary ways the body defends itself against disease.

Polyclonal antibodies are mixtures of naturally occurring antibodies expressed from different immune cells. They are extracted from human or animal blood and are used in serum or convalescent plasma-based therapies to treat diseases including COVID-19, rabies and snakebite.

Monoclonal antibodies are single antibodies expressed from identical immune cells that can be manufactured at commercial scale using cell systems. These human-like proteins are a powerful tool in treating and preventing disease.

Figure 1: Number of monoclonal antibodies approved or under review in the European Union or the United States



*Infectious diseases mAbs include five licensed in US/EU, two licensed in India, and two novel mAbs under review.

Source: Reichert (2020), The Antibody Society (www.antibodysociety.org)

compared to conventional approaches such as chemotherapy (Figure 2).

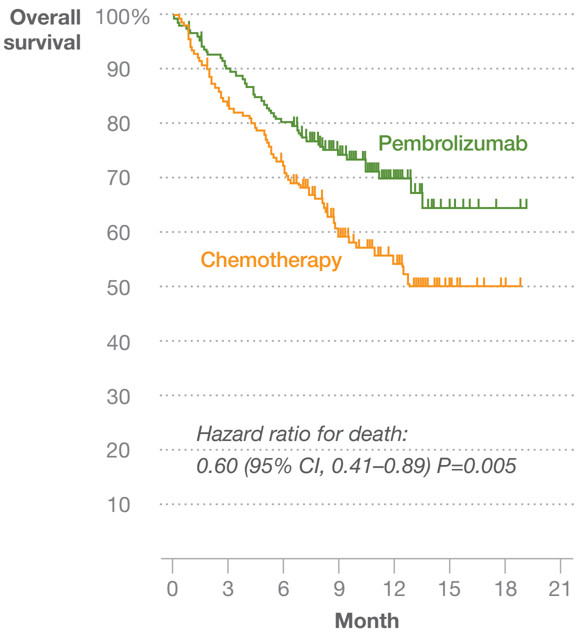
Only seven mAbs are licensed for infectious diseases.[1] But that is poised to change. There is a growing pipeline of mAbs in development for infectious and neglected diseases as well as antimicrobial-resistant bacteria, all of which are significant and escalating threats to global public health (Figure 3, next page; see Appendix, page 13).

Antibodies are now being explored for treatment and prevention of a wide range of viral diseases including Zika, dengue, Ebola, influenza, HIV and the newly identified coronavirus, SARS-CoV-2, which was first identified in China in late 2019 and was classified as a pandemic by the WHO in March 2020. Recent technological advancements have provided an opportunity to quickly isolate, develop and produce therapeutic or preventative mAbs as a complementary approach to vaccine development as part of preparing for or **responding to current and future epidemics/pandemics.**

For more, see the supplement to this report:
The emerging role of monoclonal antibodies in epidemic/pandemic preparedness and response

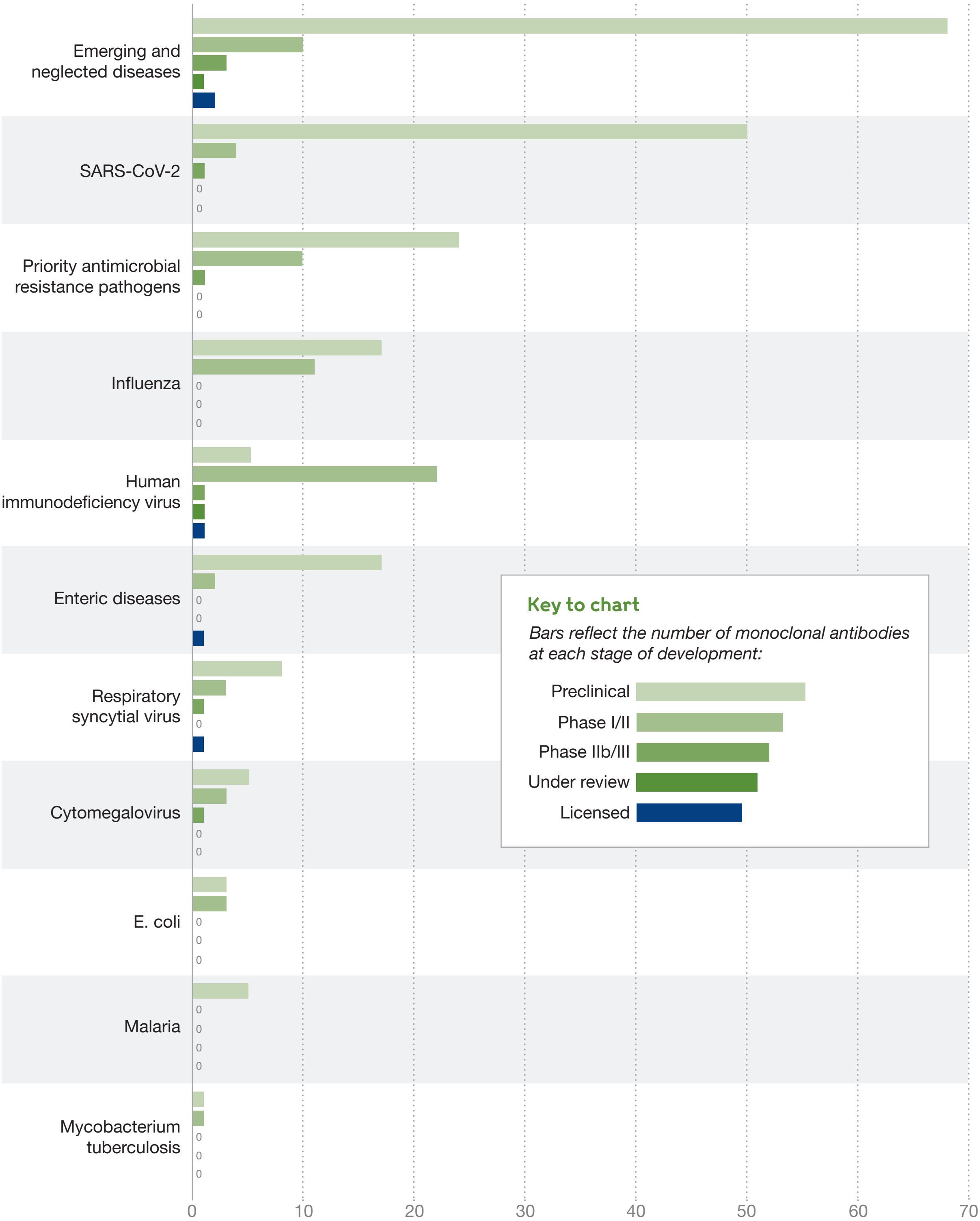
Many efforts are underway to evaluate the potential of using mAbs to treat or prevent COVID-19, and two experimental mAb products against Ebola are already being administered as part of an emergency access programme in the Democratic Republic of the Congo, where several recent Ebola outbreaks have occurred. Clinical data suggest that therapeutic Ebola mAbs[2,3], in combination with the recent approval of the first Ebola vaccine (ERVEBO®), could prove a powerful duo in treating and preventing this viral infection[4].

Figure 2: Impact of pembrolizumab in non-small cell lung cancer patients



Source: Reck (2016) N Engl J Med

Figure 3: Number of monoclonal antibodies in development and licensed for infectious diseases and pathogens



Emerging and neglected diseases are chikungunya, Crimean Congo hemorrhagic fever, dengue, Ebola, Sudan, Bundibugyo, Marburg, Junin Virus, Lassa, MERS, SARS, Nipah, Hendra, Rift Valley fever, rabies, severe fever with thrombocytopenia syndrome, Zika virus disease

Priority antimicrobial resistance pathogens are *Acinetobacter baumannii, Campylobacter, Enterobacter, Enterococcus faecium*, enterovirus, *Helicobacter pylori, Klebsiella pneumoniae, Morganella spp*, Proteus, *Providencia spp, Pseudomonas Aeruginosa*, *Salmonella Typhi, Shigella, Staphylococcus aureus, Streptococcus pneumoniae*

Enteric diseases are adenovirus, astrovirus, cholera, *Clostridium difficile*, hepatitis A, B and E, norovirus, rotavirus, typhoid

E. coli and *Klebsiella pneumoniae* are both enteric and antimicrobial resistance pathogens and are listed separately

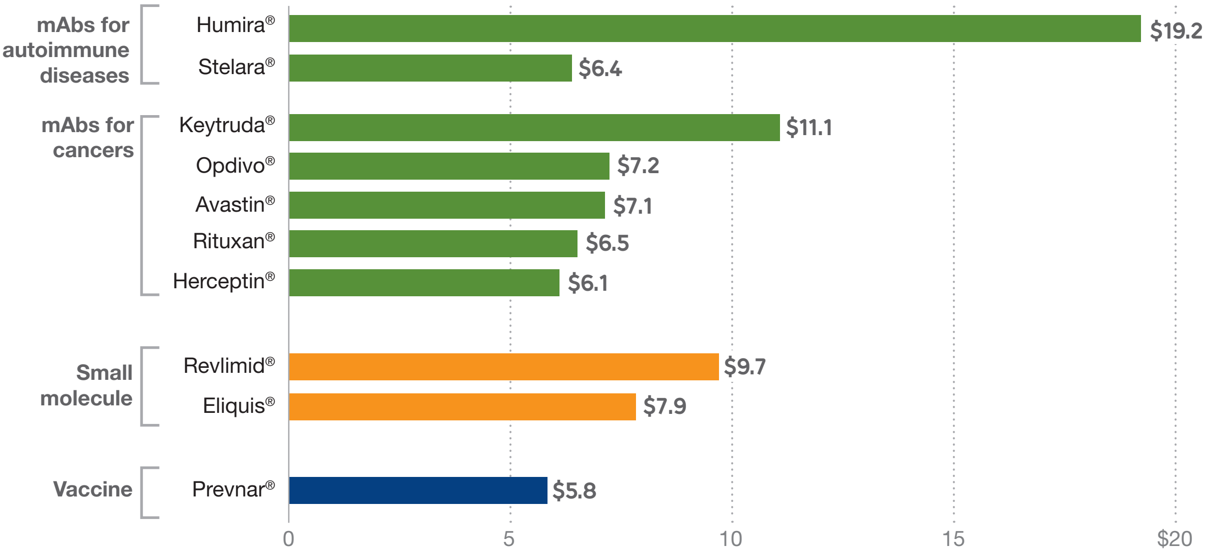
For HIV there are multiple mAbs that are being tested alone or in combination. Repurposed mabs for SARS-CoV-2 symptomatic treatment not shown. Two anthrax mAbs not shown

Preclinical numbers represent the number of institutions/programs. The clinical numbers represent numbers of antibodies, unless otherwise stated.

Source: IAVI pipeline analysis

Figure 4: Top 10 drugs by global sales, in 2019

In billions of US dollars



Source: Urquhart (2020) Nat Rev Drug Discov.

The use of mAbs to both prevent and treat HIV infection is another flourishing area of research. Several antibodies that can act against the diverse strains of the virus (so-called broadly neutralising antibodies or bnAbs) are in development and may offer new hope in battling HIV, which still newly infects about two million people each year.

For more, see the supplement to this report: *The development of HIV-specific broadly neutralising antibodies*

Data from the first proof-of-concept trial testing whether a single bnAb can prevent HIV infection is expected in 2020. Meanwhile, researchers are applying technological advances to optimise HIV-specific bnAbs and increase their potency, thereby lowering the dose necessary to provide protection in animal models[5]. Many optimised HIV bnAbs delivered subcutaneously in combination or in a single, multispecific antibody format are in development. These more potent antibodies have the potential to be more affordable globally[6].

Transforming lives, transforming markets

Given their numerous applications, the development of mAb products is one of the fastest growing segments of biomedical research. Since 1985, over 100 mAbs (Figure 3, previous page; see Appendix, page 5) have been licensed or submitted for regulatory review, with approval rates rapidly increasing. More than 50 mAbs were licensed in the last six years[1]. In 2019, seven of the ten best-selling novel drugs were mAbs for cancer and autoimmune diseases[7] (Figure 4).

Monoclonal antibodies are the single-largest class of biologic molecules undergoing clinical investigation.

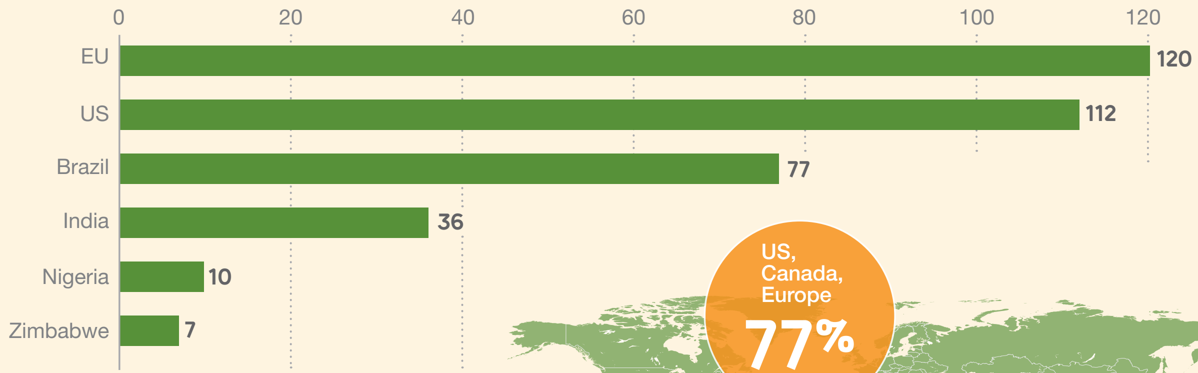
Monoclonal antibodies are also the single-largest class of biologic molecules undergoing

Global need, but not global access

Given the growing number of non-communicable and infectious diseases for which mAbs are or might be an effective treatment or preventive, there is clearly a global need for these products. Yet mAb sales are predominantly in the US, Canada and Europe (see map). Low- and middle-income countries (LMICs), which account for 85 per cent of the global population, lag far behind in mAb sales and access to these innovative products[17,20,55].

In low-income countries, few if any mAbs are even registered (see figure below). India represents one of the best-case scenarios with respect to the availability of mAbs in middle-income countries, largely because of its extensive biosimilar manufacturing capacity and the resulting competition among biosimilar products, yet even there, fewer than 22 per cent of the products in the US market are available, and no mAbs for cancer therapy are currently available in the Indian public health system[19,56]. As the percentage of mAbs in development pipelines are increasing[8], more and more mAbs will enter the market, and the disparity in access between high-income countries and the rest of the globe will likely only worsen.

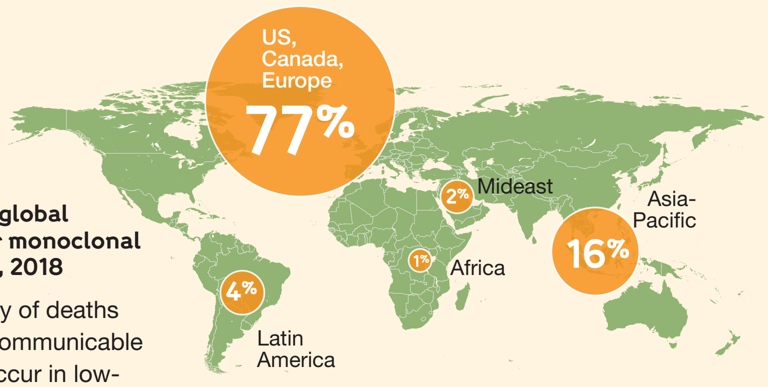
Number of registered monoclonal antibodies in selected countries (includes biosimilars)



Sources: IAVI registration analysis (chart)
Coherent Market Report, 2019 (map)

Estimated global market for monoclonal antibodies, 2018

The majority of deaths from non-communicable diseases occur in low- and middle-income countries.



clinical investigation. The percentage of biologics in development has doubled in the past two decades (increasing from 20 per cent of pharmaceutical pipelines in 1995 to more than 40 per cent in 2018)[8]. More than 570 mAbs are now in clinical testing—60 per cent of which are for oncology—and hundreds more are in preclinical development for a range of diseases[9].

Increasingly, combination mAbs are also being developed to address the emergence of drug-resistant strains or escape mechanisms for many diseases, including HIV, antimicrobial resistant infections and cancer. Combining mAb products can increase the breadth of functional activity and improve response rates[10]. There is also a growing interest in different types of antibody formats including antibody-drug conjugates (ADCs), antibody-protein fusions, antibody fragments, single-chain antibodies and multispecific formats. Multispecific antibodies offer an alternative to combinations of multiple mAbs, each binding a distinct epitope. All of these alternate antibody formats can expand the therapeutic potential of mAbs and allow for various modes of delivery[11–13].

For more, see the supplement to this report: *Combination monoclonal antibodies and alternate formats*

There is also a growing market of biosimilars, which are lower-priced versions of licensed mAbs that have no clinically meaningful differences to the originator product in terms of mechanism of action, safety, purity and potency. While somewhat akin to generic drugs, biosimilars are not identical copies of the originator mAb and, as a result, their development is significantly more complex and costlier. It is on average 50–100 times more expensive to develop and manufacture a biosimilar than a small molecule generic. It also takes eight to ten years to develop biosimilars, compared to only three to five years for generics[14].

In many countries, biosimilars enter the market once the 20-year period of patent protection on the originator mAb expires. However, in some cases, inventors can obtain secondary patents based on new uses or formulations of an existing mAb product. These secondary patents are the primary reason the introduction of biosimilars is delayed in some markets, particularly the US, where companies are more likely to file secondary patents to protect market share. Europe, India, Argentina, Brazil, Japan and the Philippines typically allow biosimilars to enter the market earlier than other countries[15].

With patent expirations for some blockbuster mAbs expected in the next few years, many companies are now developing both innovative and biosimilar mAbs[16]. Biosimilar development is thriving in India, the European Union (EU), the US, South Korea and China, with India a clear leader.

The Indian biosimilar market was evaluated at US$2.7 billion in 2018 and is anticipated to reach approximately $6.19 billion by 2024[17]. More than 100 Indian biopharmaceutical companies are manufacturing and marketing biosimilars[18], with 36 biosimilar mAb products already on the market and another 37 in the pipeline[19,20]. In 2017, Biocon, a leading Indian biosimilar company, successfully registered Ogivri® (a biosimilar of the breast cancer mAb trastuzumab) in the US in partnership with Mylan, making it the first Indian company to have a US Food and Drug Administration (USFDA)-approved biosimilar[21].

India is also a leader in developing small molecule generic drugs. Its strength and leadership in developing and manufacturing both biosimilars and generics stems partly from the country's historical intellectual property laws that did not uphold product patents. In 2005 India amended its patent laws to comply with TRIPS (Trade-Related Aspects of Intellectual Property Rights) obligations, but in the 35-year period prior to that, the country built extensive drug manufacturing capacity[22]. The Indian government also supports the development of both **innovative and biosimilar mAbs.**

For more, see the supplement to this report:
India's biopharmaceutical business: an evolving success story

Low-cost/high-volume pharmaceutical and vaccine manufacturers in India, including the Serum Institute of India Private Ltd., Gennova Biopharmaceuticals and Sun Pharma, are now investing in both biosimilar and novel mAb development, and are increasingly focused on developing products that address domestic priorities[23,24].

Globally innovative and biosimilar mAb products are a large and growing market. In 2018 the global mAb market had an estimated value of $111.7 billion. Its value is expected to increase to $319 billion by 2026[17].

Conclusion

Despite a global disease burden, access to monoclonal antibody products is predominantly restricted to high-income countries. This imbalance is preventing the vast majority of the world's population from benefiting from monoclonal antibody treatments and preventives and it is only likely to grow as more monoclonal antibodies enter the market.

Case studies: Factors affecting broader access

An analysis of select licensed mAbs is presented here to illustrate the major factors impeding more equitable global access to these products. The mAbs evaluated are for a range of infectious (RSV, *C. diff* and rabies) and non-communicable diseases (cancers and autoimmune diseases) and include both older and more recently licensed products. The priority for this analysis was evaluating access to mAbs outside of high-income countries (HICs), but in many cases, access in low-income countries was difficult to assess due to limited data. Data on non-communicable disease (NCD) mAbs are presented first as they represent the vast majority of all licensed products. While there is a rapidly growing pipeline of mAbs for infectious/neglected diseases, antimicrobial-resistant infections and emerging infections, only seven of these products are licensed and therefore access data is more limited.

Monoclonal antibodies for non-communicable diseases

Monoclonal antibody therapies are transforming the treatment of cancers and autoimmune diseases. However, access to these products, even those licensed decades ago, is still predominantly in HICs. The mAb products analysed are largely unavailable in many LMICs, despite a large and growing disease burden in these countries. The majority of deaths from leading NCD-related causes—including 70 per cent of cancer deaths—occur in LMICs[25,27], where they are now the leading cause of mortality.

In all cases presented here, lack of availability—either because the product is not registered or it is not available in public health systems—and high prices are the major factor impeding access. Lower-priced biosimilars are helping expand access in some MICs, particularly India, but prices are still too high to make them widely accessible.

HERCEPTIN®

(trastuzumab)

Company
Genentech/Roche

First approved
1988, United States

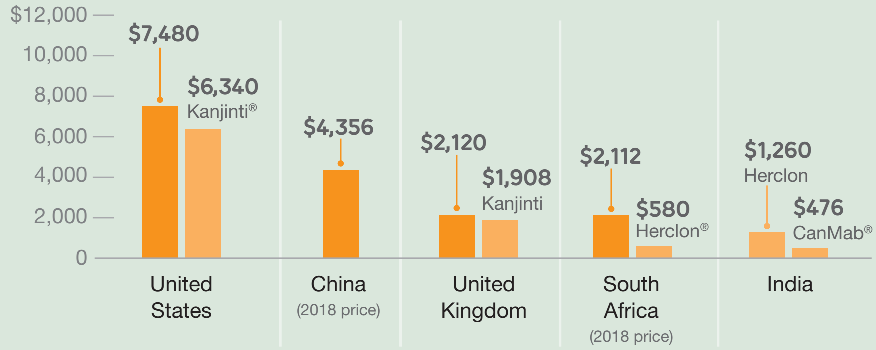
Primary indication
HER2+ breast cancer

Impact
HER2+ breast cancer has gone from worst to first because of the success of Herceptin in combination with chemotherapy

Notes: Kajinti® and CanMab® are biosimilars. Herclon® is a "second brand" of Herceptin®—a lower-priced version made by the same company but marketed with a different name and sometimes with unique packaging. Prices are as of February 2020 unless noted.

MONTHLY COST

Price of four weekly doses of 2 mg/kg for a 75 kg patient. In US dollars.



ACCESS FACTORS

- Annual costs range from $5,712 to $89,760, based on pricing data listed in different countries[28–32,98]
- Herceptin® global sales were $6.1 billion in 2019[7]
- 12% of women in the United States and 50% of women in Europe and China did not receive trastuzumab or any other HER2+-targeted agent, with price being the most significant barrier to access[33]
- A subset of oncologists in high- and upper-middle income countries reported insurance coverage, drug availability and expense were main barriers to access[34]
- A 2013 survey showed it is available at half of the healthcare facilities in 14 sub-Saharan African countries, but fewer than 5% of patients could afford it[35]
- Several biosimilars available, including four approved by the USFDA, five by the European Medicines Agency (EMA) and at least three approved products for use in low- and middle-income countries (see Appendix, page 11), but data is limited on how this has expanded access

KEYTRUDA®

(pembrolizumab)

Company
Merck

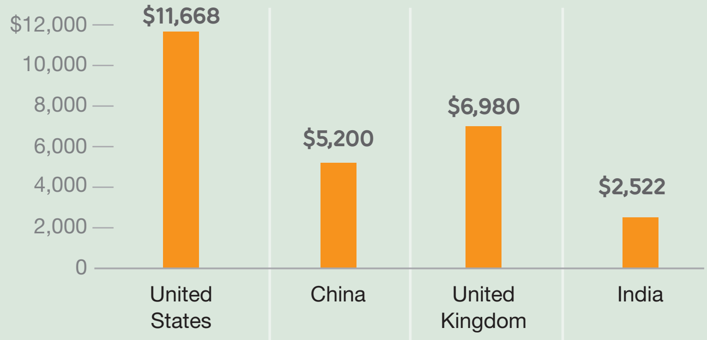
First approved
2014, United States

Primary indication
Melanoma

Impact
Keytruda® has significantly improved survival rates of melanoma, lung cancer and eight other difficult-to-treat cancers

MONTHLY COST

Price of 200 mg every three weeks. In US dollars.



ACCESS FACTORS

- Annual treatment costs range from $42,874 to $198,356[30–32]
- Keytruda® global sales were $11.1 billion in 2019[7]
- Most patients in Brazil are unable to access it through the public health system because of its high price[36]
- An oncologist in India reports "only one in 1,000 of my patients can actually afford to use this drug"[37]
- Access in public health systems and low- and middle-income countries is severely limited because of high treatment costs
- Added to the WHO essential medicines list in 2019, but unclear how this will affect access in low- and middle-income countries[38]
- No biosimilars available

HUMIRA®

(adalimumab)

Company
AbbVie

First approved
2002, United States

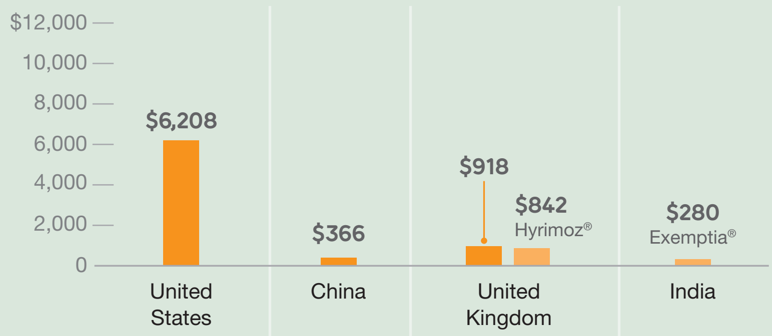
Primary indication
Rheumatoid arthritis

Impact
In patients who do not respond to conventional treatments, Humira can suppress disease activity, slow or stop progression of joint/radiologic damage and prevent further loss of quality of life

Note: Hyrimoz® and Exemptia® are biosimilars.

MONTHLY COST

Price of two doses of 40 mg every other week. In US dollars.[30-32]



ACCESS FACTORS

- Humira® is the best-selling prescription drug in the world, with sales of approximately $19.2 billion in 2019[7]
- Unavailable in India until the launch of biosimilars in 2014, despite 12 million people in the country having conditions that could benefit from its use[40]
- First available in China in 2010[39]
- Still unregistered in some sub-Saharan African countries including Zimbabwe and Nigeria
- Introduction of biosimilars in Europe in 2018 led to an 80% price reduction of Humira® in some European markets[39]
- As of 2019 there are four USFDA-approved biosimilars in the US, with another three in development, but none of them is expected to launch before 2023 when patent protection expires[20]

Monoclonal antibodies for non-communicable diseases (continued)

ENBREL®
(etanercept)

Company
Amgen/Pfizer

First approved
1998, United States

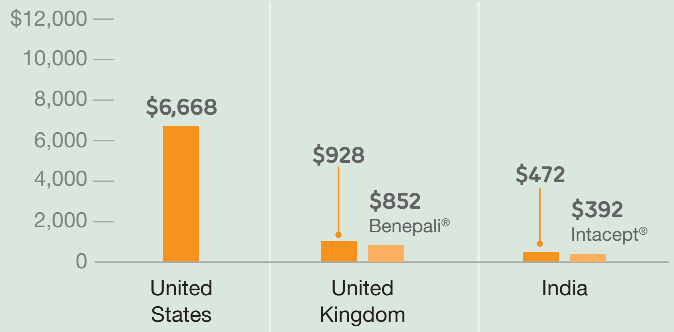
Primary indication
Rheumatoid arthritis

Impact
In patients who do not respond to conventional treatments, Enbrel can suppress disease activity, slow or stop progression of joint/radiologic damage and prevent further loss of quality of life[39]

Note: Benepali® and Intacept® are biosimilars.

MONTHLY COST

Price of four weekly 50 mg doses. In US dollars.[30–32]



ACCESS FACTORS

- Enbrel® global sales were $5.2 billion in 2019[41]
- A few biosimilars became available after expiration of the Enbrel® European patent in 2015
- Samsung Bioepis's biosimilar is approved in 38 countries but there is limited data on access[42]
- Biosimilars are unavailable in the US despite USFDA approval because of secondary patents extending until 2028 or 2029[43]

Monoclonal antibodies for infectious diseases

Availability of these select mAbs is severely limited, even in countries where the need is greatest. Where available, high prices are the biggest barrier to access, with the exception of Rabishield® and Twinrab®. Another barrier to access for some of these mAb products is that they are not optimised for use by all populations in LMICs. This analysis highlights the importance of designing and delivering infectious/neglected disease mAbs that are aligned with patient, healthcare provider and policy maker preferences. This may include antibodies that are effective against a broad range of strains (e.g., rabies) or provide longer-lasting protection (e.g., RSV).

ZINPLAVA®
(bezlotoxumab)

Company
Merck

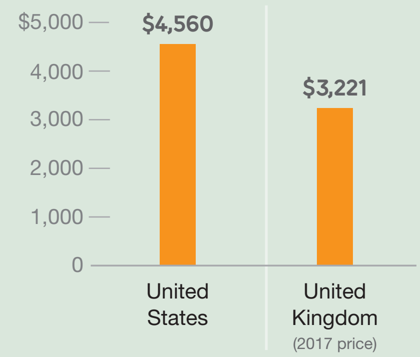
First approved
2016, United States

Primary indication
Prevention of *Clostridium difficile* infection

Impact
The only licensed mAb to prevent (in combination with antibiotics) an enteric disease. *C. diff* is the leading cause of healthcare-associated infections[47]

MONTHLY COST

Price of single-dose treatment. In US dollars.[31,44,45]



ACCESS FACTORS

- Merck is conducting clinical trials in several middle-income countries, including Colombia, Czechia, Malaysia and South Africa[46]
- No evidence of access in low- and middle-income countries
- No biosimilars available

Monoclonal antibodies for infectious and neglected diseases (continued)

SYNAGIS®
(palivizumab)

Company
MedImmune (AstraZeneca)

First approved
1998, United States

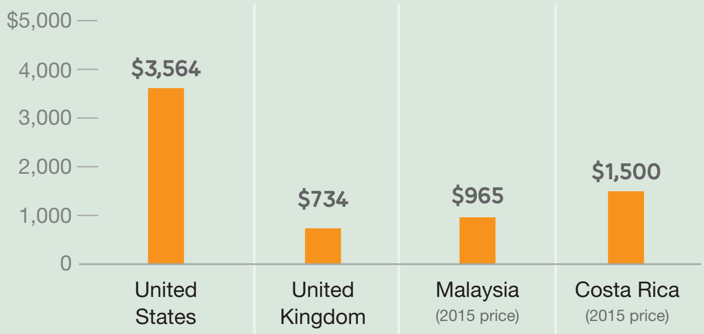
Primary indication
Prevention of respiratory syncytial virus infection

Impact
The only licensed mAb to prevent respiratory syncytial virus infections, the second-leading cause of death in children during the first year of life

Note: Prices are as of February 2020 unless noted.

MONTHLY COST

Price of a 15 mg/kg dose for a 3.5 kg patient. In US dollars.



ACCESS FACTORS

- Price ranges from about $3,600 to $17,820 per season (five doses), depending on the country[30,31,48,49]
- Marketed in over 80 countries but, 21 years after its initial approval, access in low- and middle-income countries remains limited[50]
- Not currently licensed in China or Nigeria, two countries with high[25] RSV incidence[51]
- No biosimilars available
- Access is limited by the cost and lack of inclusion on national medicines lists
- Synagis® global sales were $665 million in 2018, with more than 99% of the sales from US and EU markets despite 99% of respiratory syncytial virus deaths in low- and middle-income countries[52,229]
- Efforts are underway to develop a biosimilar that is 20-fold less expensive[53]

RABISHIELD®

Company
Serum Institute of India

First approved
2017, India

Primary indication
Rabies

Impact
Uptake has been modest so far because of competition from treatment with human rabies immune globulins/equine rabies immune globulins and a lack of assurance of a large market*

MONTHLY COST

A single dose treatment in India is priced at about $20 a vial for an ~0.2 mg/kg dose.[32]

ACCESS FACTORS

- Available in India as well as some other countries, under orphan review by USFDA
- Doesn't satisfy WHO's recommendation that a mix of at least two antibodies with non-overlapping epitopes is needed to protect against escape mutants[228]
- One of the least expensive marketed mAbs
- No biosimilars available

*Consultation with Serum Institute of India, October 2019

TWINRAB®

Company
Zydus Cadila

First approved
2019, India

Primary indication
Rabies

Impact
A combination of two mAbs expected to protect against resistant rabies strains that are not covered by the single antibody product (Rabishield®)[54]

MONTHLY COST

Anticipated price of $20 to $40 vial*

ACCESS FACTORS

- Available only in India
- Efficacy, strain coverage, price and market size will ultimately determine uptake
- No biosimilars available

*Consultation with WHO, 29 June 2020

What will it take to make monoclonal antibodies globally accessible?

To expand global access to mAbs, they must be available and affordable.

The following sections describe the barriers impeding broader access to mAbs as well as solutions to overcoming these barriers, which, if taken, could dramatically increase access and save or improve millions of lives in the process.

availability

Harmonize and expand existing policy and regulatory pathways and explore new ways to encourage wider registration of mAbs in low- and middlie-income countries

Raise awareness of the clinical, public health and economic value of mAbs through concerted advocacy efforts

Strengthen healthcare systems and the ability to diagnose disease in low- and middlie-income countries to support a more accurate assessment of the market need for mAb products and to enable their implementation

+ affordability

Validate and apply novel technologies to drive down mAb development and manufacturing costs

Implement alternate business models that prioritize access

Identify procurement and delivery models for mAbs similar to those used to increase affordability of vaccines

---

= access

Monoclonal antibodies are only accessible if they are available

Key findings:

- Many mAbs are not available in low- and middle-income countries because of long delays in regulatory filing, approval and launch of these products, which creates a huge gap in access.
- Capacity constraints, unclear or undefined regulatory policies and a lack of market incentive are all barriers to companies more broadly registering mAb products.
- Those mAbs that are registered are often still unavailable or have extremely limited availability in the public health systems in low- and middle-income countries.
- Efforts are underway to harmonise regulatory approval pathways across low-income settings.
- Of the harmonisation efforts underway, only the WHO prequalification pilot program has been applied to biosimilar mAbs, and only one mAb has been prequalified so far.
- Incorporating mAbs into WHO policy guidance is one way to support adoption of these products more globally.
- Several mAbs were added recently to the WHO's Model List of Essential Medicines, but it is too soon to tell how this will expand access.
- Advocacy efforts related to mAb access are limited or non-existent.
- Efforts to demonstrate a public health value proposition—including economic modelling of the impact of mAbs—can help bolster the case for making mAbs more widely available in low- and middle-income countries.
- Health systems strengthening and improving the capabilities to diagnose and treat disease in developing countries can help define the market size and support demand forecasting for mAb products to catalyse investments and access in these countries.
- Engaging communities, healthcare providers and policy makers will help ensure that future products are acceptable and feasible to implement in diverse settings.

One major barrier to global mAb access is that many of these innovative products are not even available in many low- and middle-income countries.

This is partly because there are long delays for filing, approval and launch of mAb products in many resource-limited settings relative to their introduction in the EU and US[55,57] (Figure 5, next page). An Access to Medicines Foundation report found that innovative products are not even registered in 43 per cent of priority LMICs, including 13 of 46 sub-Saharan African (SSA) countries.

There are several factors that contribute to these registration delays, or lack of filings altogether. One of the biggest factors is that pharmaceutical companies prioritise commercialisation in more lucrative markets in high and upper middle-income countries. Only 21 per cent of new products are filed broadly in countries identified as having the greatest need within a year of launch[55]. Addressing the

Figure 5: Regulatory approval dates for monoclonal antibodies

Country/ region	Herceptin® (trastuzumab)	Enbrel® (etanercept)	Humira® (adalimumab)	Keytruda® (pembrolizumab)
US	1998	1998	2002	2014
EU	2000	2000	2003	2015
Brazil	1999	2003	2003	2016
China	2002	2010	2011	2018
Egypt	2002	No data	2010	2016
India	2000	2002	No data	2016
Mexico	No data	2001	No data	2016
South Africa	2001	2004	2006	2017
Zimbabwe	2014	Not registered	Not registered	Not registered

Source: IAVI registration analysis

barriers to wider registration of mAbs in LMICs is a priority given the number of products in development for diseases that predominantly affect individuals in low-income settings.

Harmonising the registration process is one way to accomplish this. Regulatory requirements are often unclear or even undefined (see Appendix, page 38) in many LMICs, and variation in requirements across national medicines regulatory authorities (NMRAs) increases the cost, time and complexity for manufacturers interested in submitting their products for regulatory review[58].*

Capacity constraints pose an additional challenge. Globally, the WHO estimates that at least 30 per cent of NMRAs have limited capacity to perform core regulatory functions[59]. This gap is the widest in Africa, where the majority of the continent's 50 NMRAs are unable to perform core functions. In Kenya, the Pharmacy and Poisons Board lacks the in-house expertise to evaluate mAbs and therefore regulatory review must be outsourced.**

Some countries are taking steps to shorten their regulatory review timelines. The Chinese Food and Drug Administration (CFDA) joined the International Council for Harmonisation in 2017 and has begun to align its regulatory processes with international standards, resulting in a dramatic increase in the number mAbs approved annually. By early 2019, the CFDA had already approved three mAbs from domestic developers and 10 mAbs from multinational pharmaceutical companies, a significant increase from the average two mAbs approved in previous years[60].

Some multinational companies are also attempting to address delays in access. Novartis and Takeda have launched strategies to make their mAb products more widely available sooner after their introduction in high-income countries. For example, Novartis's mAb Lucentis® for wet age-related macular degeneration was approved in India and Brazil within 12 months of approval in the EU[57].

Another example is Novartis's approach to addressing sickle cell disease (SCD). SCD is a global health problem but the highest burden of disease is in Africa, where 50 per cent to 90 per cent of children born with the disease die before age five[61]. Novartis submitted hydroxyurea, the only USFDA- and EMA-approved drug for the treatment of SCD, to regulators in Ghana, Kenya, Uganda and Tanzania to accelerate access to treatment in communities that are most affected and plans to deliver 60,000 treatments by the end of 2020. The company also plans to file its USFDA-approved SCD mAb Adakveo®/crizanlizumab globally[62] and clinical trials are expected to start in Africa in 2020.***

*Consultation with Utrecht Centre for Affordable Biotherapeutics. 9 August 2019. Phone interview conducted by IAVI. Consultation with African Vaccine Manufacturing Initiative. 3 July 2010. Phone interview conducted by IAVI.

**Consultation with Kenyan Pharmacy and Poisons Board. 17 July 2019. In-person interview conducted by IAVI.

***Consultation with Novartis conducted by IAVI. July 2020

In addition, the company has signed agreements with the governments of Ghana, Kenya, Uganda and Tanzania to jointly develop holistic approaches to improve the diagnosis, management and effective care for SCD patients.

Despite these efforts, there are still long delays or complications to broad registration of innovative medicines and biosimilars in low-income settings. Even the definition of a biosimilar varies or remains undefined in many countries.

The EMA first established biosimilar guidelines in 2005, followed by the introduction of global guidelines through the WHO in 2009, as well as in other countries: Japan (2009), South Korea (2009), Canada (2010), the US (2012) and India (2012) have all established processes for biosimilar approval[63,65]. But many LMICs still lack a clear pathway for registering biosimilars[66]. Even the BRICS-TM (Brazil, Russia, India, China, South Africa, Turkey and Mexico) nations have less-defined regulations for biosimilar development and comparability (see Appendix, page 38).

As a result, biosimilar approval and introduction can be delayed even beyond the lengthy timeframe it takes to develop these more complicated products. The first biosimilar drug approved in South Africa, Teva's Filgrastim®, was delayed more than five years due to the backlog of products awaiting scrutiny by the South African Health Products Regulatory Authority[67]. The introduction of mAbs in India is delayed an average of five years[19], even though biosimilar development there is typically faster than in high-income countries, taking only three to five years compared to eight years in Europe[68]. Some middle-income countries such as Mexico, Nigeria and Vietnam still require in-country clinical trial data for regulatory approval or have undefined regulations, both of which contribute to delays in access[64–66].

Addressing these delays and promoting wider registration of innovative and biosimilar medicines is therefore essential. This report explores three potential solutions to expanding the global availability of mAbs:

- harmonise and expand existing policy and regulatory pathways and explore new ways to encourage wider registration of mAbs in LMICs
- raise awareness of the clinical, public health and economic value of mAbs through concerted advocacy efforts
- strengthen healthcare systems and the ability to diagnose disease in LMICs to support a more accurate assessment of the market need for mAb products and to enable their implementation.

Harmonising regulatory pathways

There are already some pathways in place to facilitate broader registrations of both innovative and biosimilar products in LMICs. These programmes include the WHO's prequalification programme, the EMA Article 58 pathway, Swissmedic and the US President's Emergency Plan for AIDS Relief (PEPFAR) tentative approval (Figure 6, next page). Prequalification has been used primarily for generic drugs and biosimilars, whereas the other programmes are designed to accelerate access to innovative medicines. Each of these efforts are designed to harmonise regulatory procedures and to help manufacturers overcome the barriers to registering their products in LMICs that may lack clear regulatory processes.

But so far these programmes have not been extensively utilised to facilitate access to mAbs. Only WHO prequalification has been used for biosimilar mAbs, and only one mAb has been prequalified to date.

The WHO prequalification system was originally set up to facilitate access to UN-supported health commodities and to address the lack of regulatory capacity in resource-limited settings. This programme aims to ensure the quality, safety and efficacy of priority global health products, while supporting capacity building for national regulatory bodies and facilitating access pathways. The first mAb—a trastuzumab biosimilar for the treatment of breast cancer—was prequalified in 2019 through a pilot procedure developed in 2018[83,230]. Prequalification of the biosimilar rituximab for the treatment of common lymphomas and leukemias is underway.

Figure 6: Collaborative and expedited regulatory pathways

Regulatory agencies/bodies	Pathways	Potential applications to antibody products
USFDA	FDA's expedited review of PEPFAR's innovative HIV products in as short as 6 months and tentative approval of generics for sale outside the US for HIV products still under US market exclusivity.[70]	HIV bnAbs
USFDA, WHO, NRAs	Collaborative Registration Procedure-Lite (CRP-Lite): facilitated through sharing of redacted assessment reports of FDA-approved products with WHO to accelerate registration of HIV medicines in low- and middle-income countries[71]	HIV bnAbs
EMA, WHO, NRAs	Article 58: EMA, in collaboration with the WHO, provides scientific opinions on medicines to prevent or treat diseases of major public health interest that are intended exclusively or initially for markets outside the EU[72]	Monoclonal antibodies for infectious/neglected diseases mainly in low- and middle-income countries
EMA, WHO, NRAs	Parallel EU and low- and middle-income country registrations: A promising initiative through which EMA collaborates with sponsors on a parallel approach that integrates elements of the Article 58 process, such as representation from WHO and low- and middle-income country NRAs during the assessment process, as part of a centralised Marketing Authorisation Application for EU registration. This pathway was tested with the recently licenced Ebola vaccine (ERVEBO®).*	Monoclonal antibodies for global health
Swissmedic, WHO, NRAs	Swissmedic (Switzerland) authorisation procedures involve African NRAs and WHO in the assessment process, building capacity and addressing regional considerations while accelerating marketing authorisations in Switzerland for Africa and elsewhere[73]	Monoclonal antibodies for global health

*Consultation with EMA. 20 September 2019. Phone interview conducted by IAVI

To address some of the barriers to access that exist even after prequalification, the WHO also developed a collaborative registration process (Figure 6) with stringent regulatory authorities (SRAs) to accelerate national registration of WHO-prequalified products. More than 20 African national regulatory authorities (NRAs) participate in WHO collaborative registration schemes, and these have resulted in registration of 152 essential medicines, cutting assessment and approval time from several years to an average of 78 days[69]. Now that a trastuzumab biosimilar is prequalified, it is eligible for collaborative registration. Most stakeholders from the African continent who were interviewed for this report agreed that products prequalified by the WHO or approved by an SRA such as the EMA or the USFDA would be more likely to be licensed quickly in their countries.

Yet even with prequalification and collaborative registration processes, some stakeholders report there are still delays in access to innovative medicines. A 2016 study showed that vaccines already approved by an SRA still took on average 16 months to complete the prequalification process[74]. Generic medicines from emerging markets took even longer—more than two years on average.

Efforts to speed approval timelines for innovative products are therefore underway through the Accelerated Registration of Finished Pharmaceutical Products Approved by SRAs procedure. Through this procedure, the assessment and inspection reports of participating reference SRAs — EMA, Swissmedic, the UK Medicines and Healthcare Products Regulatory Agency and the Swedish Medical Products Agency — and bridging reports that address issues of direct relevance in high-burden settings are shared with NRAs in 21 participating countries and the Caribbean nations in the CARICOM region. The goal is to facilitate national regulatory decisions within 90 days[75]. This procedure has resulted in 42 regulatory approvals for five different products in 20 countries, but has not yet been utilized for mAb products. Many other challenges also remain, including addressing inconsistent requirements across NRAs that required supplemental documentation and additional inspections.

One effort to support regional harmonization of NRAs is the African Medicines Agency (AMA). In 2019, 55 African nations signed the treaty to form the AMA, which will promote the adoption and harmonisation of regulatory policies and standards and will coordinate existing harmonisation efforts[76]. The aim of the AMA is to align fragmented regulatory systems on the continent, reduce the lead time associated with meeting different country requirements and increase the availability of safe, effective and high-quality essential medicines for priority and neglected diseases across the African continent[77]. The AMA will provide an important platform to address some of the regulatory barriers impeding access to biologicals in Africa[78].

Another effort to support harmonisation is the African Vaccine Regulatory Forum (AVAREF), a regional regulatory network founded by the WHO in 2006 with 23 African member-countries. AVAREF aims to support NRAs in their decision making by providing information on vaccine candidates and timelines for clinical trials, and also to promote communication and collaboration between African NRAs and ethics committees[79]. Although only applicable to vaccines, AVAREF could be a model for supporting regional NRAs for mAb regulatory issues.

Funders such as the Bill & Melinda Gates Foundation and Unitaid are also supporting efforts to facilitate regulatory approvals of priority global health products in LMICs. Unitaid is supporting efforts to ensure that innovative biologics are promptly produced and accessible in LMICs. They are partnering with the WHO, UN agencies and product developers to support prequalification and to allow for rapid scale-up of high-quality, affordable biologics in these countries.* These efforts will be particularly important for countries that eventually transition from receiving assistance from global health organisations such as The Global Fund, to a reliance on domestic funding.

Additional efforts to harmonise registration pathways for mAbs in LMICs may also be required to ensure broad availability of these products in developing countries.

Expand and utilise policy pathways for mAb access

WHO policy guidance also plays an important role in the adoption of new technologies and their integration into financing and procurement platforms. Some stakeholders that were interviewed noted that many LMICs will not include a medicine on their national medicine lists or utilise a treatment or therapy unless it is part of WHO guidelines.**

It can therefore be beneficial for mAb developers to engage with the WHO early in the process if they are interested in having their products included in WHO policy guidelines and securing prequalification. This engagement allows the WHO to provide guidance on the preferred attributes of an eventual product as well as its potential value proposition and access pathways, all of which can help favorably position products for a policy review that occurs post licensure[80].

Preferred Product Characteristics (PPCs):
Most companies that develop mAbs design target product profiles based on the needs of individuals in high-income countries. This can result in products that are not as well suited for use in LMICs because of factors such as their dosing regimen, side effects or feasibility constraints[81]. To avoid this, the WHO is developing PPCs to provide strategic guidance on the preferred attributes for new vaccines and antibodies in priority disease areas. PPCs are developed as part of a broad consultation process early in clinical development. Considering the needs of individuals outside of high-income countries early in the mAb development process—when product attributes can be more readily changed—can help ensure that products satisfy end-user preferences and pricing expectations, and that they can be implemented in places with more limited healthcare infrastructure.

Technology Roadmaps and Full Public Health Value Propositions:
Technical documents such as these outline priority activities for researchers, funders and product

*UNITAID consultation. 31 July 2019. Phone interview conducted by IAVI.

**Global Fund and PEPFAR consultation. 17 June 2019. Personal interview conducted by IAVI; WHO and UNAIDS consultation. 29 May 2019. Phone interview. Interview conducted by IAVI; UNITAID consultation. 31 July 2019. Phone interview conducted by IAVI.

Figure 7: Monoclonal antibodies included in the WHO Model List of Essential Medicines

Antibody	Brand name	First approved indication	WHO EML inclusion year
Adalimumab	Humira®	Rheumatoid arthritis	2019
Certolizumab pegol	Cimzia®	Crohn's disease	2019
Golimumab	Simponi®	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2019
Infliximab	Remicade®	Crohn's disease	2019
Nivolumab	Opdivo®	Melanoma, non-small cell lung cancer	2019
Pembrolizumab	Keytruda®	Melanoma	2019
Rituximab	MabThera® Rituxan®	Non-Hodgkin's lymphoma	2015
Trastuzumab	Herceptin®	Breast cancer	2015
Bevacizumab	Avastin®	Colorectal cancer*	2013

*WHO EML for age-related macular degeneration, not licensed for this use. Source: WHO (2019) Model List of Essential Medicines

developers to accelerate the availability of products in priority disease areas and to articulate the economic, societal and indirect impact of the intervention at the population level.

Together, these guidance documents can facilitate the inclusion of a mAb product in formal WHO guidelines[80]. This approach is primarily used for development of new vaccines, but in recent years the WHO has provided some preliminary guidance on preventative mAbs for RSV and rabies in the context of available vaccines, and the organisation is now involved in drafting the first formal PPCs for HIV and RSV mAb products.

Adding mAbs to the WHO's Model List of Essential Medicines (EML) is another way to influence national policies and encourage broader uptake of mAbs. Inclusion on the EML can affect eligibility for reimbursement through public health systems[82], and can help ensure these products are integrated into procurement and supply channels.

Avastin® (bevacizumab) was the first mAb added to the EML in 2013 for off-label treatment of age-related macular degeneration (Figure 7). In 2015, Rituxan® (rituximab) and Herceptin® (trastuzumab) became the first two cancer mAbs to be added to the EML. These mAbs were added long after their initial approval, but in the last two years, 18 antibodies were reviewed and six were added to the EML in 2019 alone.*

The growing number of mAbs on the EML is spurring efforts within the WHO, relevant UN agencies and international organisations to facilitate access to these products[83]. Inclusion of mAbs on the EML should encourage more countries to add them to their own essential medicine lists—more than 155 countries create national essential medicines lists based on the EML[38].

However, delays are still likely as national lists may not be updated as regularly. Kenya first established its essential medicines list in 1981, but has only updated it four times since then[84]. Despite Avastin's inclusion on the EML in 2013, and Herceptin and Rituxan being added in 2015, there is limited evidence that these mAbs are widely included on national medicine lists and therefore the impact on global access is unclear[85]. Addressing the barriers (including patent protection and registration) to nations adding mAbs on the WHO EML to their own essential medicine lists will help raise awareness of the value of mAbs and enhance access in LMICs.

In addition to the EML and other WHO policy pathways, health technology assessment (HTA) bodies that perform value-based assessments of innovative medicines and help determine pricing (see page 30) could also be used to influence which mAbs are included on national medicine lists. HTAs in some LMICs such as China, Thailand and Tanzania are already being utilised this way[86–88].

*WHO and UNAIDS consultation. 29 May 2019. Phone interview conducted by IAVI.

Raise awareness of the health benefits of mAbs

Advocacy is essential to promoting supportive policy regarding mAbs and to enhance availability. Yet advocacy for mAb products is either limited or nonexistent. The unprecedented advocacy that played a vital role in expanding access to HIV medicines and preventives in developing countries could serve as a model. A similar movement could help bolster the case for global mAb access.

Underpinning all efforts to make mAbs more widely available is the need to increase awareness among governments, ministries of health and patient advocacy groups of their transformative health benefits, both on the individual level and the public health level. As governments struggle to prioritise healthcare interventions, advocacy efforts will be critical to making political leaders and public health officials aware of the broad potential mAbs offer to treat and prevent diseases.

Related to this, advocacy efforts could help dispel the misperception that mAbs are too expensive to ever become widely available in LMICs. Some mAbs are already available at much lower prices, and by implementing a combination of innovative technologies and alternative business models (see page 28), these prices could be even lower, making them more affordable for more of the world. Global access to mAbs will not be easy, but it is possible, and advocacy efforts will be required to deliver that message.

Cost-effectiveness and health economic modelling of the impact of mAbs can also help inform advocacy efforts by establishing a value proposition for introducing mAbs more broadly, particularly within the public health systems of LMICs. For cancer, mAb products could even be introduced before older medical options, “leapfrogging” radiation treatment and chemotherapy, which are more challenging to implement in resource-poor settings[89].

Another component of advocacy for mAb access is ensuring that mAbs receive widespread support through their inclusion in UN-backed global public health agendas, such as the Sustainable Development Goals and Universal Health Coverage (UHC). UHC, which was adopted in 2015, calls for all individuals and communities to receive health services without suffering financial hardship. Including mAbs in such agendas can spur government investment and stimulate industry focus on delivering affordable and accessible mAb products. Major public health funders, including Wellcome through their Flagship initiative, the Bill & Melinda Gates Foundation, Unitaid and the Coalition for Epidemic Preparedness Innovations (CEPI) are either already considering or could consider adding mAb development to their portfolios.

Strengthen healthcare systems and the ability to diagnose disease

Improving capabilities to both diagnose and treat disease is another important component of improving global access to mAbs.

Gaps in local health systems and inadequate infrastructure hamper the delivery of medicines to millions of people and delay access to innovative medicines such as mAbs.

This is particularly true for products to treat non-communicable diseases. Most deaths from non-communicable diseases occur in LMICs, where 85 per cent of the global population lives[25,26]. Cancer services and access to diagnostic medical equipment are limited in these countries (Figure 8, next page) despite a large and growing disease

In many countries there are not enough specialists, experts or specialised medical centers for specific diseases.

burden. In many countries there are not enough specialists and/or specialised medical centers for specific diseases[90]. For example, Zambian cancer patients must travel to South Africa and pay out of pocket to access mAb cancer treatments, an option only viable to wealthy individuals.*

The burden of many diseases is also unknown or measured inaccurately in many LMICs, including Kenya and Zambia, because of limited medical staff, training and diagnostic equipment[90,91,99]. Strengthening healthcare systems and the ability to diagnose disease will help provide mAb manufacturers with a more accurate assessment of disease burden and the market size for their products in LMICs, which is a critical component of expanding access to mAbs.

For infectious diseases, expanding the availability and rapid use of diagnostic tests confirming the type and strain of pathogen is also critical to ensuring timely and appropriate treatment. To enable broader use of therapeutic mAbs, diagnostic capabilities for infectious diseases will also need to be strengthened.

Figure 8: Pieces of medical equipment per million population in 2013

Country	Magnetic resonance imaging	Radiation therapy
Japan	45.94	7.17
Canada	7.99	8.07
Mexico	1.41	0.54
Yemen	1.15	0.12
Honduras	1.11	0.74
Zimbabwe	0.28	0.42
Afghanistan	0.10	0
Uganda	0.08	0.05
Cambodia	0.07	0.07
Zambia	0.07	0.04
Central African Republic	0	0

Source: WHO (2016) Global Health Observatory data repository

*Personal communication with Professor Chipeta at the University of Zambia and IAVI

Making monoclonal antibodies more affordable

Key findings:

- mAbs are unaffordable for most of the world's population.
- Companies focused on high-income country markets have little incentive to pursue lower-cost strategies to develop, manufacture and deliver mAbs.
- Competition, regulation and other strategies that can lower mAb prices are not sufficient to make these products affordable globally.
- Advancements in antibody optimisation, manufacturing technologies and packaging and delivery have the potential to lower mAb production costs and increase efficiency.
- Local and mobile manufacturing of mAbs are untested in LMICs but may be an alternative for improving access to affordable mAbs in remote areas.
- Creative intellectual property/licensing frameworks may help expand access to mAbs.
- Alternate business models, including public-private partnerships and industry-led access models, are emerging to support mAb research and development, manufacturing and global access for non-communicable and infectious/neglected diseases.
- Including mAbs in pooled procurement platforms, similar to those used for vaccines, could make them more widely accessible.

One barrier to achieving global access to innovative mAbs is that they are unaffordable for most of the world's population.

Biologics, and particularly mAbs, are among the highest priced pharmaceutical products in the world[7]. In the US, biologic drugs represented 2 per cent of all prescriptions in 2017, but 37 per cent of net drug spending[93]. The median price for mAb treatments in the US ranges from approximately $15,000-$200,000 a year[31] (Figure 9, next page). And mAb-based therapies are increasingly prescribed in sequence or in combination, which can result in even higher treatment costs.

The most expensive mAbs are for oncology and hematology, with annual treatment prices approximately $100,000 higher than mAbs for other diseases[94,95].

Drug prices, including those for mAbs, vary greatly worldwide because of a variety of factors (see page 30). But with few exceptions, existing price-control mechanisms and access strategies are insufficient to make mAbs widely affordable (Figure 10, next page).

The same is true for biosimilars. The introduction of lower-priced biosimilar mAbs can offer significant savings to payers and governments that are struggling to prioritise healthcare interventions and manage already stretched budgets. But, to date, biosimilars have not expanded access substantially. This is because they are still largely unaffordable[53,100].

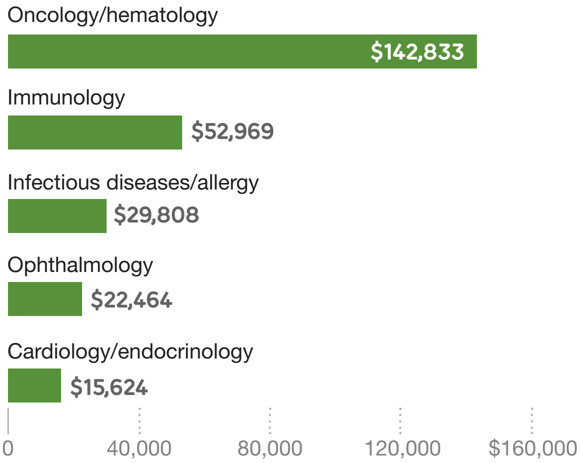
In most countries, generic drugs are typically sold at steep discounts—more than 90 per cent off the original price—whereas biosimilars are generally only 10 per cent to 35 per cent less expensive than the originator mAb in most countries. This difference is explained, at least in part, by the fact that biosimilars are much more complicated and costlier to develop than small molecule generics (see page 13).

Even in India, where biosimilar prices are discounted the most because of extensive local production and competition among biosimilar manufacturers, they are discounted by 57 per cent—significantly less than generic drug discounts[14,31,57,101].

The WHO estimates that up to 90 per cent of the population in LMICs purchase medicines through out-of-pocket payments[102]. Therefore, even at a substantial discount, mAbs and biosimilars remain too expensive for many people. Also, few, if any, of the most commonly prescribed mAbs are reimbursed through public health systems even in some middle-income countries, such as Kenya, India and Egypt (Figure 10)[56,96,97,103].

Figure 9: Median price of monoclonal antibodies by therapy area for one year of treatment

US prices as of January 2017, in US dollars

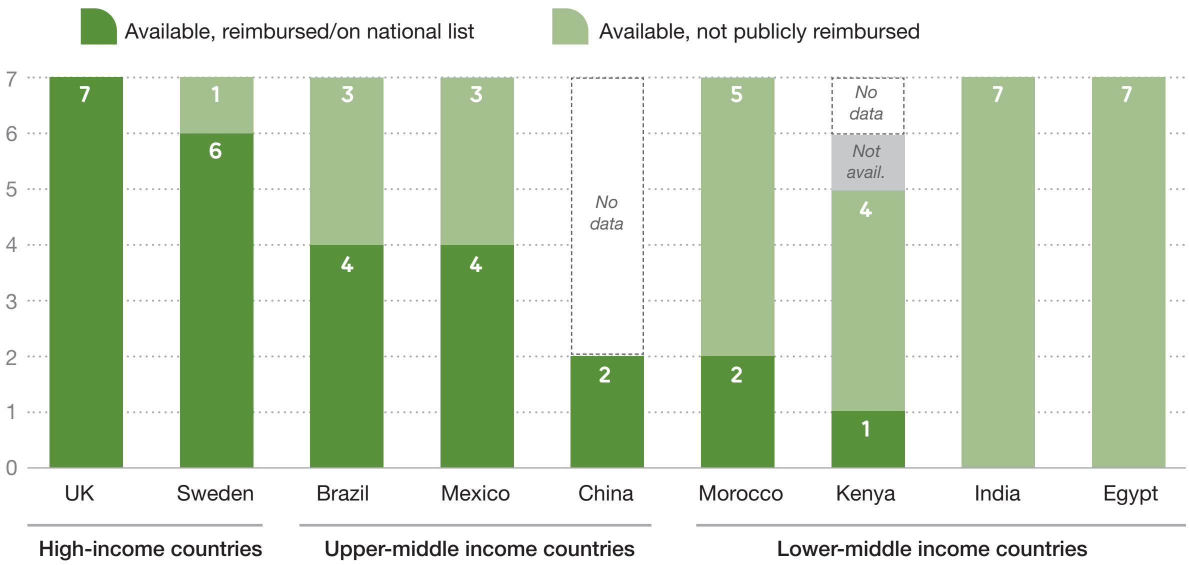


Source: Hernandez (2018) Am J Manag Care

This report focuses on three potential solutions, which if applied in combination, could make mAbs more affordable:

- validate and apply novel technologies to lower mAb development and manufacturing costs
- implement alternate business models that prioritise access
- identify procurement and delivery models for mAbs similar to those used to increase access to vaccines.

Figure 10: Availability of seven monoclonal antibodies* in selected countries with different levels of universal health coverage, 2018



*Adalimumab, cetuximab, ipilimumab, panitumumab, pertuzumab, rituximab, trastuzumab. Note: "not avail." = not available/not registered

Source: WHO (2018) Pricing of cancer medicines and its impacts

Factors influencing global mAb prices

Several factors influence drug prices, and how they are applied varies in different parts of the world. As a result, drug prices can also vary widely (Figure 11, next page). Some of the most common factors that affect global mAb prices are:

1 COMPETITION among products for similar indications or with similar mechanisms of action can impact price, as can competition from biosimilars.

Competition in the Indian biosimilar market has led to biosimilars that are priced up to 70 per cent lower than the local retail price of the innovator mAb. In some cases, biosimilar competition can even spur manufacturers to lower the price of the originator antibody to retain market share. Dr. Reddy's Laboratories biosimilar Reditux® (rituximab) was introduced in India at 50 per cent less than the retail price of Roche's Rituxan/MabThera® (rituximab)[104]. In response, Roche lowered the price of Rituxan® to promote its brand-name product[104].

2 INTERNATIONAL REFERENCE PRICING (IRP) is one of the most common price-control mechanisms used by governments. It uses the proposed price of a product in several countries to derive a benchmark or reference price.

The potential downside of IRP is that it may cause companies to delay or avoid launching new drugs in countries that use IRP, especially if they are small markets referenced by countries with larger markets. One study showed that pharmaceutical companies systematically delayed submission in Belgium because of IRP[105].

3 COST-EFFECTIVENESS THRESHOLDS are used to determine the acceptable price based on a product's clinical effectiveness.

Health technology assessment (HTA) mechanisms are increasingly used to make value-based assessments of medicines and to inform both pricing and reimbursement decisions. HTAs are usually conducted by independent government agencies such as the National Institute for Health and Care Excellence in England, the Canadian Agency for Drugs and Technologies in Health or the National Committee for Health Technology Incorporation (CONITEC) in Brazil. One drawback to HTAs is that they are time-consuming processes that can delay patient access, particularly for products that receive conditional regulatory approval based on limited clinical data[106]. And in some countries, like Spain and Italy, autonomous regions and hospitals sometimes conduct their own HTA and negotiations with manufacturers after national decisions, leading to further delays[107,108].

Risk-sharing agreements between the payer and a company can also be used when there is uncertainty associated with the efficacy of a drug. Risk-sharing agreements allow payments to be determined based on the clinical benefit of a product. Risk-sharing agreements have improved access to select medicines in some European countries, including Sweden, Portugal and Italy[109,110].

More than 25 European countries have a national HTA and the Japanese government recently announced plans to implement one[111,112].

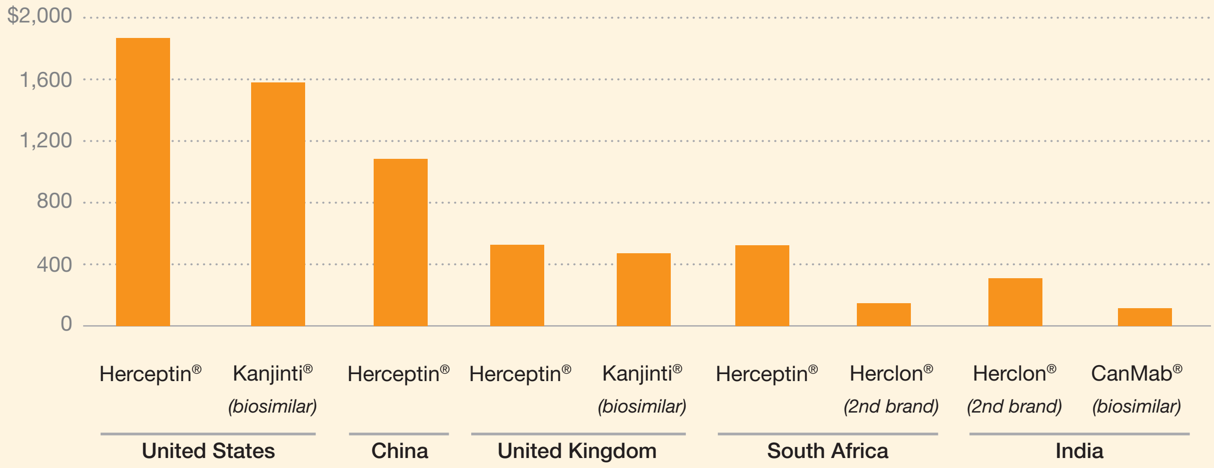
Efforts to establish HTA-like groups are also emerging in some African countries. With the support of the International Decision Support Initiative, the KEMRI-Wellcome Trust Research Programme is supporting the development of an HTA mechanism in Kenya. Most participants in stakeholder meetings convened in Zambia, Uganda, Kenya and South Africa agreed that establishing HTA bodies to assess mAbs would be useful; however, they cautioned that there may not be enough skilled personnel to form these advisory bodies, especially in smaller African countries. As an alternative, they suggested establishing more regional HTAs that could evaluate data from countries with similar disease burdens and demographics.

4 TIERED PRICING is a strategy used to set prices for different parts of the world based on macroeconomic indicators, such as the average national gross domestic product per capita. Tiered-pricing levels are often established through direct negotiations between government payers and manufacturers.

Tiered-pricing arrangements vary across companies, therapy areas and products. They are currently being applied in Kenya to increase patient access and affordability to Roche's cancer mAb trastuzumab[113]. In 2016 Roche agreed to provide trastuzumab to the Kenyan government at 50 per cent off its normal price. The Kenyan government then agreed to establish a small fund (initially valued at $195,000) to help patients pay the remaining treatment costs[114].

Figure 11: International comparison of Herceptin® (trastuzumab) prices

Price per dose of 2 mg/kg for a 75 kg patient, in US dollars



Sources: 28–32

This programme is attempting to make a cancer mAb more affordable in a country where 75 per cent of the population lacks private health insurance[115].

5 **DIRECT PRICE NEGOTIATIONS between pharmaceutical companies and governments or procurement bodies can provide assurance of significant market volume, which ultimately can be an incentive for manufacturers to lower their prices.**

China is increasingly relying on direct price negotiations to determine drug prices for national reimbursement[116]. The National Development and Reform Commission now sets a maximum reimbursement for products on the National Reimbursement Drug List (NRDL). Only those products included on the NRDL are eligible for provincial tenders. Manufacturers are therefore incentivised to lower prices to be included on the NRDL, and then to lower prices even further to win provincial tenders. Trastuzumab was launched in China in 2002 and Roche reduced the price of the mAb by roughly 70 per cent to get it included on the NRDL in 2017[29,117].

6 **INTRODUCTION OF SECOND BRANDS is a way for companies to market lower-priced versions of an originator mAb in a specific market, such as public health systems in LMICs.**

Second brands have a different name and use unique supply chains, sometimes including the use of local manufacturers, to further differentiate them from original brands and to prevent lower-priced products from threatening profitability in high-income country markets. Introducing second brands can also increase competition.

In some cases, second brand strategies and alternate supply chains have led to more affordable mAb prices in middle-income countries. In South Africa, Roche sells its breast cancer mAb trastuzumab as both Herceptin®, the original brand, and as a second brand called Herclon®. Herclon® is sold for $145 per dose—a 70 per cent discount off the price of Herceptin®—and is only available within the public health system[28]. In India, Roche only sells the lower-priced, second brand Herclon®. This has given rise to increased biosimilar competition. The biosimilar CanMab®, manufactured by the Indian company Biocon, is available in India at a substantially lower price than Herclon® (Figure 11).

In India, Roche partnered with the local manufacturer Emcure to produce and market second brand versions of two of their mAbs: Herclon® and Mabthera®, a second brand of Rituximab®[118].

In many instances, these pricing factors are applied in an integrated manner. In Brazil, for example, regulators use both IRP and value-based assessments based on advice from the national HTA agency CONITEC[119]. A manufacturer must prove that a new medicine offers clinical benefits over a comparator to be able to charge a premium price. If deemed innovative, IRP is then used to derive the drug's list price. The average price of the mAb trastuzumab dropped by 57 per cent after it received CONITEC approval in 2012[120].

Validate and apply novel technologies to lower costs

The process of developing new medicines is long and costly. It's reported to cost on average $2.6 billion to develop a new drug[121], although the precise costs associated with developing any specific product are undisclosed. Pharmaceutical R&D is also a high-risk business as many drug and vaccine candidates fail in clinical testing.

In the US, where prescription drug prices are the highest, there is no clear association between research and development costs and drug prices[122]. Companies that market many of the originator mAbs are primarily focused on markets in high-income countries, where prices are the highest. Given this, there is limited incentive for companies to devise lower cost strategies for developing or manufacturing mAbs in an effort to lower prices[123].

It reportedly costs between $95–$200/gram to produce marketed mAbs, with even higher costs for startup companies, and this does not take into account research and development costs[14]. However, there are several innovative technologies that could be applied across the mAb development continuum—from discovery to delivery—which, if coupled with alternate business models, could substantially reduce mAb development and production costs as well as prices.

Selection and optimisation

Advances in B-cell immortalisation, high-throughput screening, single-cell analysis and display technologies, and humanised animal models (see Appendix, page 34) have made it possible to rapidly identify antibodies—including rare and potent antibodies from currently or previously infected humans—that bind to specific targets.

Technological advances are also making it possible to engineer mAbs to improve their potency, breadth, half-life and biophysical properties[5,124]. For example, clinical studies of the anti-RSV antibody MED18897-YTE and the anti-HIV antibody VRCO1-LS have demonstrated that slight modifications can lead to four- to fivefold enhancements in half-life, which is anticipated to translate into products that can be delivered less frequently, on average once every three to six months[5,124]. More recently, an integrated approach of deep sequencing, bioinformatics and directed evolution by yeast display is being utilised to select and optimise antibodies with biophysical characteristics that would make them more amenable to manufacturing[125].

For example, Just Biotherapeutics, which was recently acquired by Evotech Inc., uses software to predict how modifying the DNA sequence of a protein could increase its drug-like properties and expression in cell culture, thereby making it easier to purify and manufacture. The company, with support from the Bill & Melinda Gates Foundation, is developing their technology to develop sequence-optimised broadly neutralising HIV mAbs with improved stability that could be manufactured at low cost[126].

Manufacturing

Currently, most commercial mAbs are produced in mammalian Chinese Hamster Ovary (CHO) cells that are engineered to produce a large quantity of

> "Improvements in mAb potency and reduced manufacturing costs would reduce the dosage and frequency of administration, leading to decreased cost and improved convenience."
>
> Gary Nabel, CSO and Senior Vice-President, Sanofi Inc.

antibodies (in the 1–5 gram/liter range)[123]. CHO cell lines expressing the antibody of interest are typically grown in large bioreactors for more than 10–15 days. The resulting antibodies are then purified through multiple-column chromatography methods[127] and formulated for appropriate administration, a process called "batch production." CHO cells make fully functional proteins that are generally well tolerated by humans, but they require a long production time and high material costs.

To reduce cost and increase capacity, many manufacturers are therefore exploring alternatives to batch production methods. Continuous biomanufacturing and single-use bioreactors are two technologies that can improve the speed, flexibility and convenience of CHO-based mAb production[128]. Single-use bioreactors allow for a quicker turnaround, can be used in tandem to produce biopharmaceuticals at scale and require significantly lower capital investment to construct. This technology has enabled the development of global mAb production facilities.

Integrated continuous biomanufacturing processes are also faster and cheaper[129], and offer more consistent processing and greater product quality. Economic analyses of continuous biomanufacturing coupled with continuous chromatographic processes (referred to as integrated continuous processing) can reduce costs by 55 per cent compared to conventional batch processing, considering both capital and operating expenses[128].

WuXi, a leading mAb manufacturer based in China, runs the world's largest disposable bioreactor-based biologics manufacturing facility. The facility uses a continuous bioprocess system integrated with single-use bioreactors that is predicted to reduce mAb manufacturing costs from $95–$200 per gram to less than $15 per gram, or $3 for an average 200 mg dose of most mAbs[130–132]. If these efforts to dramatically lower production costs are coupled with a dramatic reduction in price, it would be a big step towards making mAbs more affordable.

The Serum Institute of India is also investing in more efficient manufacturing processes with multiple modular facility units at a new site in Pune, India, to support their growing investments in both biosimilar and innovative mAb development and manufacturing[133].

Many alternatives to CHO-based mAb production are also being explored[134] (Figure 12). Alternate production platforms, including yeast, fungus, algae and transgenic plants, as well as nucleic acid delivery via DNA or messenger RNA (mRNA; Figure 13, page 35) have the potential to be cheaper and faster than traditional methods. Using genetic constructs—either DNA or mRNA—as a delivery system could reduce production costs by five- to tenfold[135].

Packaging and delivery

The way mAb products are packaged and delivered can also help lower mAb production costs. Delivery of mAbs is complicated by their physiochemical and biological properties. Most antibodies are delivered

Figure 12: Alternative monoclonal antibody manufacturing methods

Method	Manufacturer	Programmes	Highest status of programmes	Advantages and challenges
Yeast	Alder Biopharmaceuticals	Migraine and chronic autoimmune diseases	Submitted to USFDA for approval	Lower upfront investments and lower cost of production; glycosylation patterns and post translational modifications can be a challenge; however, GlycoFi engineered strains more human-like — but no recent activity reported[136,137]
	Research Corporation Technologies	Contract work	Available for licence	
	GlycoFi (Merck)		Unreported	
	Numerous groups in research: Genomics Research Center; Academia Sinica Taiwan; Scripps Research; MIT		Preclinical	

(table continues on next page)

Figure 12: Alternative monoclonal antibody manufacturing methods (continued)

Method	Manufacturer	Programmes	Highest status of programmes	Advantages and challenges
Transgenic tobacco	Mapp Biopharmaceutical; LeafBio	Ebola, HIV	Phase II	Lower upfront investments as smaller facilities needed, but variation in quality[138–140]
	PlantForm	Cancer, Ebola HIV, ricin, undisclosed	Preclinical	
	Planet Biotechnology Inc.	Common cold	Discontinued Phase II	
	Fraunhofer Institute for Molecular Biology	HIV	Phase I	
	iBio	RSV, Ebola	Preclinical	
Fungus	Dyadic with Serum Institute of India	Undisclosed	Undisclosed	Higher yield per liter of media and potential for lower cost; engineering of more human-like strains ongoing[141]
Milk of transgenic cattle	China Agricultural University	Cancer	Preclinical	Lower upfront investments but glycosylation challenges[142]
***In vitro* cell-free expression systems**	Sutro Biopharma	Cancer	Preclinical	Potential for lower cost; however, large-scale production untested[143]
Algae	Institut de Recherche et d'Innovation Biomédicale	Hepatitis B	Preclinical	Low production costs; challenges with heterogeneity and post-translational modification[144–147]
	Scripps Research; University of California, San Diego	Cancer, anthrax, HSV, botulism	Preclinical	
	Algal Research Group; University College London	No mAb data		
Baculoviral insect cell	Vienna Institute of Biotechnology; University of Natural Resources and Life Sciences	HIV	Preclinical	Potential for lower cost; however, large-scale production untested[148]
Silkworm baculovirus expression	National Institute of Health Sciences, Kanagawa	Cancer	Preclinical	Potential for lower cost; however, large-scale production untested[151]
Drosophila S2 cell line	Institut Pasteur of Shanghai	Influenza	Preclinical	Potential for lower cost; however, large-scale production untested[149]
***In situ* vector gene delivery**	IAVI	HIV	Phase I	Potential for lower cost; however, undetectable expression in clinical study (lack of proof of concept)[150]
	NIAID	HIV	Phase I	Ongoing POC (NCT03374202)

Table doesn't include data for SARS-CoV-2 mAbs

Figure 13: DNA and mRNA monoclonal antibody delivery

		Target	Antibody	Organisation
mRNA clinical				
	Emerging diseases	Chikungunya virus *First in class*	mAb	ModernaTX Phase I NCT03829384
mRNA preclinical				
	Oncology	Lymphoblastic leukemia	mAbs and bispecific T cell engagers	BioNTech[152]
		Non-Hodgkin's lymphoma	mAb	CureVac AG[153]
		Breast cancer	mAbs and bispecific T cell engagers	Inovio Pharmaceuticals[154]
	Infectious diseases	HIV	mAb	University of Pennsylvania[155]
		HIV, influenza B, rabies	mAb	CureVac AG[153]
		RSV	mAb, VHH	Emory University[156]
	Toxins	Botulism	VNA/VHH	CureVac AG[153]
DNA clinical				
	Emerging diseases	Zika *First in class*	mAb	Inovio Pharmaceuticals Phase I NCT03831503
DNA Preclinical				
	Emerging diseases	Ebola (Zaire)	mAb	Wistar Institute[157]
		Dengue	mAb	University of Pennsylvania[158]
	Infectious diseases	HIV	mAb	Wistar Institute[159]
		Influenza A and B viruses	mAb	Wistar Institute[160]
	AMR	Pseudomonas aeruginosa	mAb	Wistar Institute[161]

VHH = variable domain of heavy-chain-only antibody. VNA = VHH-based neutralizing agents. AMR = antimicrobial-resistant diseases
Table doesn't include data for SARS-CoV-2 mAbs

either intravenously, subcutaneously or in some cases through nasal administration if the mAb is susceptible to gut protease degradation. Intravenous (IV) administration has several drawbacks: it is more complicated, it can be more painful and therefore less tolerable for recipients, and it is more expensive as it must be administered by a medical professional. Studies have found that IV administration of trastuzumab is associated with a more than twofold higher administration cost (not including the cost of the mAb)[164].

Alternate administration routes are therefore one way to reduce delivery costs. Subcutaneous injection is a less expensive way to administer mAbs. About one-third of all mAbs approved in the past ten years are administered via subcutaneous injection[165].

Some manufacturers are also researching more patient-friendly and cost-effective delivery devices, including microneedles and slow-release implants (Figure 14, page 37). Additional investments and innovation are needed to create convenient and affordable devices that are more amenable for global use.

Technologies that enable oral delivery of mAbs are also in development. Most mAbs are of the naturally occurring immunoglobulin G (IgG) subtype[1]. This subtype of mAbs is relatively stable and has long half-lives, which makes it suitable for large-scale manufacturing. But the naturally occurring IgA2 mAb subtype is resistant to mucosal proteases and enzymes, making them amenable to oral delivery. In preclinical murine challenge studies, oral delivery of IgA2 mAbs protected against enteric bacteria including *Salmonella*, *Shigella* and *E. coli*[166,167]. These IgA2 mAbs have shorter half-lives and are more challenging to manufacture[168], so new technologies are being developed to address these shortcomings. For example, heavy-chain variable domain nanobodies that are engineered to be resistant to intestinal and inflammatory proteases have been delivered orally and shown to survive in the intestinal tract of humans with intestinal bowel disease[169, 170].

For more, see the supplement to this report: *Combination monoclonal antibodies and alternate formats*

A proprietary spirulina algae-based production and oral delivery technology is also being tested in preclinical studies for the delivery of single-chain camelid antibodies for diarrheal diseases[171]. Researchers are isolating antibodies from humans that could be delivered orally for the treatment of serious diarrhea and intestinal inflammation caused by *C. diff* infections[172]. Other technologies that could allow for oral delivery of antibodies for enteric and liver diseases are also in development[173].

In addition to the route of administration, innovative approaches to packaging and storage can also help make mAbs more affordable. Blow-Fill-Seal technology, a form of advanced aseptic packaging in which the container is formed, filled and sealed in one automated system, has recently been used for injectables and biologics, including vaccines and mAbs[174]. Blow-Fill-Seal technology replaces glass vials or pre-filled syringes—typically used for subcutaneously administered mAbs[175]—with plastic, which reduces accidental breakage. The low-cost, aseptic design and compact nature of Blow-Fill-Seal tubes, which can be custom made for a wide range of volumes and readily shipped, could help achieve broader access to mAbs.

Shipping and delivering mAbs is also complicated because they are typically less stable at ambient temperatures and therefore require cold storage. Maintaining cold-chain facilities can be challenging in some parts of the world. In Africa, cold-chain systems are primarily used for storing and shipping childhood vaccines and there's little additional capacity. Cold-storage systems also add to the expense of delivering mAbs, particularly in low-income countries that contend with frequent power outages. Products that require freezing temperatures for transport and storage would pose a challenge in many countries, according to stakeholders. Therefore, technologies that could reduce the cost of monitoring and maintaining cold-chain systems* as well as developing alternate thermostable formulations of mAbs that would enable storage at ambient temperatures could also help make mAbs more affordable and accessible.

Mobile manufacturing

More flexible and modular units are also being developed to manufacture biologics. These mobile manufacturing units could be particularly useful in local outbreak situations. However, these technologies have not yet been tested or used for the local production of quality-controlled, affordable biologics in an LMIC setting.

- Univercells's miniaturised bioreactors are easily transportable and could enable in-country mAb production by deploying low-footprint, multiproduct facilities that are more affordable to build and operate[162].
- Emergent BioSolutions Inc. is developing a mobile, small-scale manufacturing site for biologics that is designed to manufacture mAbs in a controlled environment the size of a shipping container that could be deployed wherever an outbreak occurs[163].
- Research is also advancing in the field of benchtop manufacturing. Some groups are developing small automated systems capable of producing clinical-grade therapeutic proteins, including mAbs, in a matter of days. These fast and flexible manufacturing processes could be performed in a hospital or a pharmacy and could enable the production of small amounts of mAbs for endemic breakouts, with limited, if any, cold chain storage. The Massachusetts Institute of Technology (MIT) is developing the Integrated Scalable Cyto-Technology, a closed system of producing and purifying biologics using *Pichia pastoris* yeast cells. This platform has the potential to shorten production times by tenfold[163].

How all of these technologies are applied—whether it is optimising antibodies to lower the dose, using alternate manufacturing platforms or developing oral formulations—will ultimately determine how much lower mAb costs can be. Alternate business models will also need to be implemented to ensure that lower production costs result in lower prices. Other factors will also need to be considered, including the disease in question, the existing treatments available, what is feasible in various LMIC settings and what is acceptable to the populations that will ultimately use these products. Understanding the preferences of communities, healthcare workers and

*Consultation with Southern African Programme on Access to Medicines and Diagnostics. 17th July 2019. In person interview conducted by IAVI.
Consultation with CAPRISA. 19 July 2019. Phone interview conducted by IAVI

Figure 14: Examples of advancements in mAb delivery

Advancement	Device or technology	Antibodies
Large volume subcutaneous delivery	Halozyme ENHANZE: Drug delivery technology based on recombinant human hyaluronidase PH20 enzyme, rHuPH20, which locally degrades hyaluronan in the subcutaneous space; allows for increased dispersion and absorption of co-administered therapies enabling large volume (>5 ml)	Roche with Halozyme has developed two cancer mAbs; Herceptin Hylecta® (trastuzumab) and Rituxan Hylecta® (rituximab)[176]
Large volume on-body infusors	Pushtronix System—The device adheres to the body, usually on the abdomen, and patients are hands-free during administration; 420 mg/3.5mL of Repatha® is delivered subcutaneously in nine minutes	Amgen's Repatha® (evolocumab) single dose monthly dosing for cholesterol lowering[177]
	enFuse is an on-body infusor drug delivery device designed for patient self-administration of high-volume drugs from 5 to 50 mL	Enable Injections is in development partnerships with Genetech, Sanofi, and Apellis Pharmaceuticals for mAb delivery[178]
Slow release subdermal	Medici Drug Delivery System: A matchstick-sized osmotic mini-pump designed to deliver a continuous flow of medication placed under the skin for once- or twice-yearly dosing	Intarcia and Numab collaboration focused on the development of once- or twice-yearly mono-specific and multi-specific antibodies addressing diabetes, obesity and autoimmune indications[179]
Microneedles	Transdermal alternative for drug delivery using micron-scale needle structures	In preclinical development, testing bevacizumab and PD1 antibodies[180–182]
Electroporation	Electroporation uses very short electrical pulses to produce temporary pores of nanometer-range diameters in the intercellular lipid matrix of the skin, which allows for the delivery of large molecules	Inovio's Dengue/Zika mAb delivered with their CELLECTRA® 2000 device is in Phase I clinical testing NCT03831503
Jet injectors	Jet injectors are a needle-free drug delivery device that delivers the biologic through a pressurized liquid, clinically shown to be less painful and preferred by patients compared to a standard needle-based injection	Takeda Pharmaceutical and Portal Instruments in development for Entyvio® (vedolizumab)[183]

policy makers can help guide the development of products that are acceptable, affordable and feasible to implement.

Local production, local access

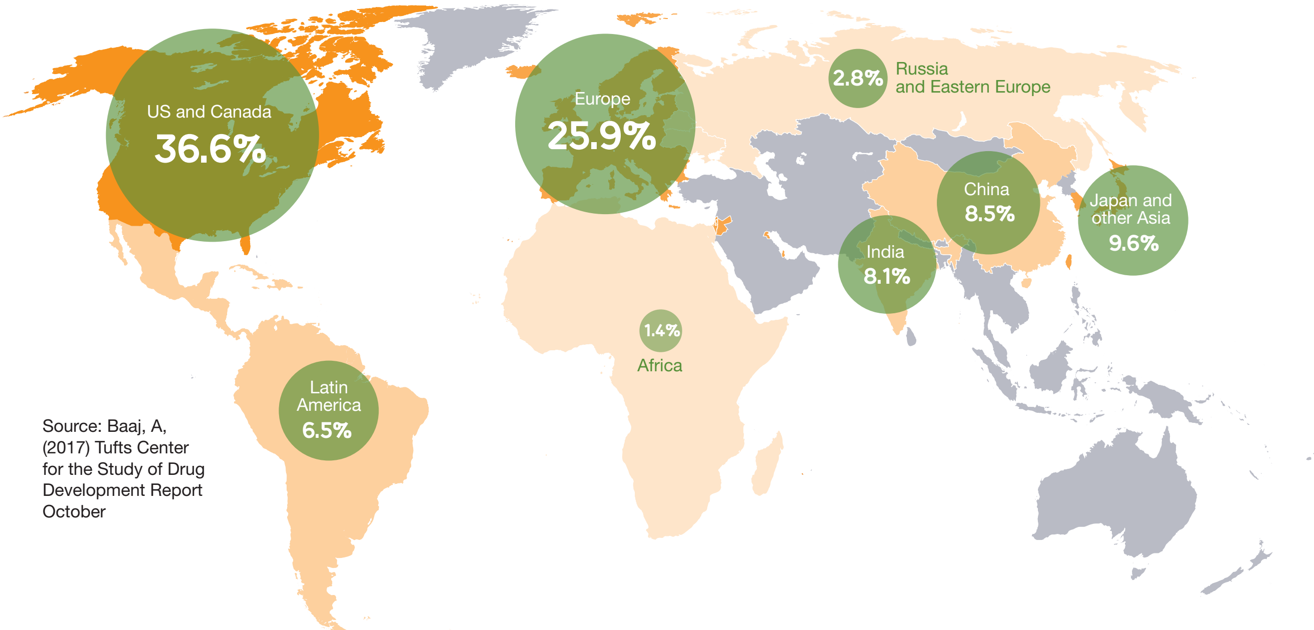
Another way to increase access to mAbs is to expand local or regional manufacturing capacity.

It's estimated that around 79 per cent of all pharmaceuticals in Africa are imported[184]. Importation can increase costs and lead to delays in access, or even drug shortages. But the economic benefits of local manufacturing are dependent on large volume demand[128]. And maintaining the quality of the facility and mAb product and aligning manufacturing standards with local regulatory expectations can be complicated.

Many MICs are capable of manufacturing small molecules and vaccines[185], but manufacturing of biologics, including mAbs, mostly occurs in North America and Europe (Figure 15, next page)[186]. However, the number of mAb manufacturing facilities is expanding in Asia and South America. India now has more USFDA-approved manufacturing facilities than any country except the US[187] and their mAb manufacturing capacity is growing.

Africa currently lacks the capacity to produce mAbs locally. Some stakeholders highlighted the need to train and develop personnel required for the production and regulation of biologics before

Figure 15: Concentration of global biopharmaceutical manufacturing



Source: Baaj, A, (2017) Tufts Center for the Study of Drug Development Report October

Examples of monoclonal antibody manufacturing facilities in Asia, Africa and South America

Manufacturer	Country	Method of production	Status
mAbxience	Argentina	Single-use bioreactor	Operational[188]
PlantForm	Brazil	Plant transgenic	Development unreported[189]
Butantan	Brazil	Continuous processing	Under construction[190]
Libb	Brazil	Single-use bioreactor	Operational[191]
WuXi Biologics	China	Single-use bioreactor	Operational[131]
Pfizer	China	Single-use bioreactor	Under construction[131]
Boehringer Ingelheim	China	Single-use bioreactor	Under construction[192]
WuXi Biologics	China	Continuous processing	Operational[193]
HJB	China	Continuous processing	Operational[194]
Biocon	India	Hybrid model (undisclosed)	Under construction[195]
Cipla	India	Continuous processing	Operational[196]
Fujifilm	Japan	Continuous processing	Operational[197]
Lonza	Singapore	Single-use bioreactor	Operational[198]
WuXi Biologics	Singapore	Continuous processing	Under construction[199]
iBio	South Africa	Plant transgenic	Unreported[200]
Cipla	South Africa	Single-use bioreactor	On hold[201]

investment in local manufacturing in Africa could be considered.*

One of the main challenges, according to stakeholders, is that the market size for mAbs in many African countries is largely unknown, and without the guarantee of a large market, local manufacturing is not feasible. “When it comes to antibodies, unless you have a big market it’s really not viable to set up [local manufacturing]. It’s only when you produce very large volumes that you can drop your prices.”**

*Consultation with KEMRI-Wellcome Trust. 4 June 2019. Phone interview conducted by IAVI. Consultation with African Vaccine Manufacturing Initiative. 3 July 2010. Phone interview conducted by IAVI. Consultation with Clinton Health Access Initiative. 5 July 2019. Phone interview conducted by IAVI. Consultation with Kenyan Pharmacy and Poisons Board. 17th July 2019. In person interview conducted by IAVI. Consultation with Southern African Programme on Access to Medicines and Diagnostics. 17th July 2019. In person interview conducted by IAVI.

**Professor Salim S. Abdool Karim, FRS Director: CAPRISA Professor of Global Health: Department of Epidemiology,

Innovative approaches to intellectual property to expand access

One potential approach for facilitating greater access to mAbs and biosimilars in LMICs is the use of voluntary licences. The Medicines Patent Pool (MPP), founded in 2010 by Unitaid, has successfully utilised voluntary licences from pharmaceutical companies to enhance access in LMICs to drugs to treat HIV, TB and hepatitis C. Upon securing the voluntary licence from a pharmaceutical company for a specific compound, the MPP sublicenses the patent rights to manufacture and commercialise the drug to one or more generic manufacturers to support specified LMIC markets that have been agreed upon with the pharmaceutical company.

MPP undertook a feasibility study with the WHO to assess whether they should expand their mandate to include other infectious and non-infectious diseases that impact LMICs, as well as biological products, including mAbs[202]. They concluded that the MPP mechanism could enhance access to biosimilars in LMICs, particularly for products with sizeable markets, such as for the treatment of breast cancer, provided that the technology transfer could be negotiated together with a licence. MPP plans to release a special report on biologics soon.

TRIPS agreements allow for compulsory licences and exemptions to intellectual property protection for life-saving medicines in low-income countries. But compulsory licensing has mostly been used for procurement of HIV/AIDS therapies in LMICs and has not significantly improved access to other medicines in the least-developed countries[203,204]. Compulsory licensing has not yet been utilised to broaden access to mAb products and there may be challenges to utilising this approach.

Some public-private partnerships are using intellectual property rights to ensure that any products developed through their collaborations will be promptly registered, manufactured in adequate quantities and distributed at reasonable prices in developing countries. An increasing number of public and philanthropic funders, including Wellcome, are requiring similar access provisions for R&D they support[205].

Implement new business models that prioritise access

Not all mAb products on the market today are priced at thousands of dollars per dose. Biocon's Canmab® — a biosimilar version of the breast cancer mAb Herceptin®—sells for $100–$200 per dose in India, significantly less than the $1,800 price per dose in the US. Innovative products Rabishield and Twinrab, as illustrated on page 17, are priced at approximately $20–$40 per dose. These examples provide proof of concept that mAbs can be sold at dramatically lower prices while still maintaining a viable, albeit lower-profit business model.

For mAbs to be globally accessible, prices may need to be even lower. How much lower will ultimately vary by country and disease area, but the goal is to ensure that affordability is not a barrier to access for more of the world's population.

Efforts to lower mAb development and manufacturing costs are essential to making mAbs more affordable. But alone, they are not sufficient. Access-driven, innovative business models are also necessary. By both implementing new technologies and developing sustainable lower-profit business models, mAbs could be made more affordable. Public-private partnerships such as the Utrecht Center for Affordable Biotherapeutics (UCAB) and companies like the Serum Institute of India already aim to reduce mAb production costs, and prices, substantially. UCAB is targeting a price of $50 per dose for palivizumab, more than 20-fold less than the average price of Synagis® in high-income countries, while some low-cost manufacturers are targeting prices as low as $5 per dose.*

Other models of collaboration between multinational pharmaceutical companies, governments, low-cost manufacturers and procurement agencies will also be required to ensure that both existing mAbs and those in development are made more affordable.

*Stakeholder consultation with lost cost Indian manufacturer

Alternate funding models to stimulate research and development for infectious/neglected diseases

For some infectious/neglected diseases and drug-resistant bacterial infections, the burden is overwhelmingly in developing countries and so there is not a strong market incentive for pharmaceutical companies to invest in this research. As a result, alternate funding models are filling the gap. Today, development of new therapies for infectious and neglected diseases is mainly supported by public-sector and philanthropic sources[206], which are creating alliances with governments, private companies and other public-sector entities to support mAb research and development.

The public sector provided nearly two-thirds of the global infectious/neglected disease R&D funding in 2016, with contributions from the US, UK and European Commission topping the list. The US was by far the largest funder, providing $1.5 billion in funding in 2016, nearly three-quarters of the global total[207].

Philanthropic entities including the Bill & Melinda Gates Foundation and Wellcome also provide significant levels of R&D funding for infectious and neglected diseases. The Bill & Melinda Gates Medical Research Institute, a non-profit biotech organisation, is focused on advancing products, including mAbs, to fight malaria, tuberculosis and diarrheal diseases[208]. Wellcome, through their Innovations Flagships, is committed to a broad portfolio approach to address neglected, tropical and infectious diseases, and is exploring the affordability of mAbs and their potential role in enteric disease treatment and prevention. Wellcome also has specific initiatives in epidemics, drug-resistant infections and snakebite.

Other funding sources include:

- CARB-X (Combating Antibiotic Resistant Bacteria)—a non-profit partnership financing the development of therapies, prevention and diagnostics that target high-priority drug-resistant bacteria[209]. CARB-X is supported by multiple public and non-governmental organisation (NGO) sources and has supported two mAb projects so far: funding Visterra Inc. to develop VIS705, a novel broad-spectrum antibody-drug conjugate against multiple drug-resistant strains of *Pseudomonas*[210], and funding Bravos Biosciences for the preclinical development of antibodies for multidrug resistant *E. coli* strains[211].

- The European Commission's Innovative Medicines Initiative (IMI) supports many research consortia to jointly develop new antibiotics as well as alternatives such as mAbs[212]. The COMBACTE-NET (combating AMR in Europe) network[213], supported by IMI, is conducting a phase II trial of MEDI3902, an investigational bispecific mAb owned by Medimmune against *Pseudomonas aeruginosa.*

- Venture capital initiatives, such as the Impact Repair Fund by Novo Ventures[214] and the AMR Diagnostic Challenge[215].

- LifeArc, a leading UK medical research charity, has partnered with Kymab, a clinical-stage biopharmaceutical company, to develop mAb-based therapeutics for a range of targets[216].

- Some governments are also exploring a "Netflix"-like subscription-based model to incentivise R&D. The UK's National Health Service will test the world's first subscription-style payment model to encourage pharmaceutical companies to develop new drugs for drug-resistant infections[217]. It works like this: Instead of paying companies based on the volume of medicine sold, the government will make upfront payments to pharmaceutical companies for access to their drugs based on their usefulness.

Access-focused alternate business models

A few of the alternative business models currently being used to develop more affordable mAbs are described below.

Utrecht Centre for Affordable Biotherapeutics (UCAB)
The WHO and Utrecht University in The Netherlands initiated a technical collaboration in 2014 to create UCAB[53]. UCAB is pioneering access models to develop high quality and affordable biotherapeutics through an association of distributed manufacturers in MICs.

UCAB's first pilot project, with technical oversight and in-kind contributions from the WHO, is to develop a low-cost biosimilar version of Synagis® (palivizumab) against RSV with an anticipated estimated price of $250 per child for a full course of fives doses[53]. UCAB has created a consortium, including a lead manufacturer (mAbxience) and local manufacturers (Libbs in Brazil, Medigen in Taiwan and Spimaco in Saudi Arabia) to support the project. UCAB anticipates filing the palivizumab biosimilar in 2023[53]; however, determining market size is a key challenge,* especially if a new, single-dose mAb for RSV becomes available by then.

IAVI
IAVI is working with partners to launch a set of initiatives to make mAb treatments and preventives affordable and globally accessible. IAVI's strategy is to enable wider access to mAbs through innovation and investments in product development and optimisation, low-cost manufacturing and novel business models. IAVI, in collaboration with Scripps Research, has been a leader in the discovery and optimisation of potent HIV-specific bnAbs for prevention and treatment. Much of IAVI's work on HIV bnAbs has been supported by the US Agency for International Development[218].

IAVI is also partnering with the Serum Institute of India to produce affordable and accessible HIV bnAbs, as well as other mAb products[219]. With support from the UK Department for International Development, IAVI has formed a research consortium on snakebite to identify and engineer antibodies to treat envenoming, a disease caused by snake venom[220]. IAVI and its partners are also applying their experience in HIV to the discovery and development of mAbs to prevent and treat a variety of emerging and established infectious diseases including drug-resistant bacteria and COVID-19[221].

MIT BioACCESS
The development of new health technologies for NCDs is predominantly led by pharmaceutical companies. Although NCDs are now the most common cause of death and disability worldwide, accounting for 70 per cent of global mortality, there has not been a significant expansion of resources or attention from international donors or governments to address this escalating disease burden in developing countries[222]. In 2017, development assistance for health from major funding sources (bilateral assistance, philanthropies, NGOs, etc.) totaled over $37 billion, while funding for NCDs was less than $1 billion)[206].

MIT BioACCESS, part of the MIT's Center for Biomedical Innovation, is addressing the complex issues surrounding global access to biologics, in particular for NCDs in resource-constrained settings. Through an "Access-by-Design" framework, this group is utilising a systems-based approach to model the impact different innovations could have on manufacturing and delivery of NCD biologics. Such models are anticipated to highlight the factors that directly influence affordability and availability at a local level.

MIT BioACCESS has so far focused on building the biomanufacturing component of their model. MIT's Center for Biomedical Innovation has developed two pre-competitive consortia related to biomanufacturing. These initiatives bring academia, industry and regulatory authorities together to better align incentives and work in ways that can advance the objective of providing sustained access to more patients.**

Industry-led access models

Pharmaceutical companies are critical to planning for and supporting access to existing mAbs in developing countries. An important component of industry-led access initiatives in LMICs are patient-access schemes. These schemes between payers (including ministries of health, private insurance companies and procurement agencies) and pharmaceutical companies started out in high-income countries, but are now increasingly being used in middle-income countries in Latin America, Asia and Africa to enable patient access to innovative medicines.

One type of patient access scheme that is more common in developing countries is company-led, patient-assistance programmes. These programmes seek to increase access to innovative medicines and address a lack of healthcare infrastructure.

Both Roche and Takeda have launched patient-assistance programmes to provide mAb therapies to patients who couldn't otherwise afford them. Roche is partnering with the governments of China, Pakistan and the Philippines to supply their breast cancer mAb Herceptin®[113]. In Pakistan Roche splits 50 per cent of the cost of Herceptin® treatment with the federal government for patients in need.

In China, the company collaborates with the Cancer Foundation (CFC) and the Ministry of Health to donate eight cycles of Herceptin® after the patient has completed the first six cycles. Before this programme fewer than 15 per cent of women in the public health system in China received Herceptin®. Now, more than twice that amount complete the full course of treatment. To date, over 60,000 women

*Consultation with Utrecht Centre for Affordable Biotherapeutics. 9 August 2019. Phone interview conducted by IAVI.

**Consultation with MITBioAccess team. 15 and 29 August 2019. Phone and email interviews conducted by IAVI.

have accessed Herceptin® through this programme, which has also made Chinese physicians more willing to prescribe the mAb[223].

Takeda's access strategy focuses on providing some of the company's most innovative medicines as well as strengthening local R&D and healthcare capacity in LMICs. The company offers patient-assistance programmes in 14 countries in Asia, Africa, Latin America, the Middle East and Europe. As a result of these programmes, Takeda has provided more than 125,000 patients with treatment, screened over a million patients for cancer, hypertension and diabetes, and trained over 4,000 healthcare providers and community health workers to improve patient care[224].

Nearly 700 patients have been treated with Takeda's most innovative antibody-based medicines — Adcetris®, an antibody-drug-conjugate for relapsed and refractory Hodgkins lymphoma, and Entyvio®, a mAb product to treat inflammatory bowel disease[224]—as a result of these patient-assistance programmes.

The affordability of Adectris® and Entyvio® were assessed by an independent third party, Axios, which created an individualised payment scheme for each patient to ensure they could complete their entire course of treatment even if they could not pay for it in full. This personalised pricing is distinct from standard discounts or tiered pricing. The patient-specific approach takes into consideration what is an affordable price for each individual, rather than determining it more broadly on a country or even community level. This patient assistance programme is a useful case study for access to novel mAb therapies, and if scaled up and applied to other mAbs, could have a significant impact on global access.

Takeda's Access to Medicines (AtM) R&D initiatives also aim to share knowledge and build skills to strengthen local R&D and healthcare capacity in LMICs. This includes supplying medical and scientific equipment and developing research capabilities[224].

Other multinational companies are also starting to recognise the need for access strategies to provide innovative medicines, including mAbs, in LMICs. The Access to Medicines Foundation's (AMF) recent ten-year analysis noted that companies are gradually changing their business models and are setting access targets for products outside of high-income countries[225]. However, only a few companies so far are supporting comprehensive access agendas (covering R&D, pricing, manufacturing, distribution, licensing, capacity building and product donations), and only a limited number of diseases and countries are covered.

Establish procurement and delivery models to enable greater acess

Access to existing health technologies for infectious diseases in low-income countries and some middle-income countries is largely facilitated by government and philanthropic funding pooled through UN-backed agencies like Gavi (vaccines), The Global Fund (HIV, TB and malaria) and UNICEF (children's wellbeing), or the US government-supported PEPFAR programme (HIV). Pooled procurement is akin to buying in bulk—these agencies combine several buyers (typically governments of various countries) into a single entity and purchase vaccines or medicines on behalf of those buyers at discounted prices. Pooled procurement has helped make vaccines and medicines available and affordable in the poorest countries in the world[226]. However, mAbs are not yet included in any of these existing donor-funded procurement agencies.

Gavi, the Vaccine Alliance, which was established in 2000, gathers large-scale donor funding (approximately $9.1 billion from 2016-2020)[227] and uses it to fund the purchase and procurement of vaccines for the poorest nations in the world. Gavi considered providing mAb-based post-exposure prophylaxis (PEP) for rabies but instead decided to support rabies vaccines for PEP beginning in 2021[228]. Gavi also considered supporting mAbs for prevention of RSV, but initially supported RSV vaccines and not mAbs.

Still, a Gavi-like financing model, which has been highly successful for childhood vaccines, could be a viable solution for broadening access to mAbs.* Gavi and The Global Fund are both considering including mAbs in their long-term planning,** and it is anticipated that UN-backed procurement agencies, specifically those involved in vaccines, may eventually support procurement of mAbs.*** However, as UN-backed procurement agencies depend upon prequalification by the WHO, their ability to support procurement of mAbs will be limited unless more mAb products undergo the prequalification process.

Other agencies involved in drug procurement, including The Global Fund, are open to considering including mAbs for infectious/neglected diseases in their long-term planning.**** Other procurement models will likely also be required to widen access to mAbs for non-communicable diseases.

*Consultation with Churches Health Association of Zambia. 4 July 2019. Phone interview conducted by IAVI

**Consultation with GAVI, 4 July 2019. Consultation with The Global Fund .17 June 2019. Phone interviews conducted by IAVI

***Consultation with UNICEF 13 September 2019. Phone interview conducted by IAVI. Consultation with The Global Fund 17 June 2019. Phone interview conducted by IAVI

****Consultation with GAVI, 4 July 2019. Consultation with the Global Fund.17 June 2019. Phone interviews conducted by IAVI

A roadmap for expanding global access to monoclonal antibodies

Monoclonal antibody-based therapies are unavailable and unaffordable for millions of people around the world. The goal of this report is to catalyze new ways of thinking, greater collaboration and new ways of doing business to address this inequity.

The following roadmap details specific actions to expand access to existing monoclonal antibodies for both non-communicable and infectious diseases and to pave the way for expeditious development and introduction of future monoclonal antibody products. If the desired outcomes are reached, there will be substantial progress towards advancing global access.

GOAL 1

Increase the availability of mAbs in low- and middle-income countries

PART I: ADVOCACY

Monoclonal antibodies save lives: Spread the word

Action > Increase awareness among governments, ministries of health and patients that mAbs have substantial clinical and public health value

Who's needed > *Government agencies, global health organisations, academic and public research institutions, funders, non-profit product developers and bio-pharmaceutical industry, non-governmental organisations (NGOs) and civil society groups*

Bolster advocacy efforts related to mAb access in low- and middle-income countries

Government agencies, global health organisations, academic and public research institutions, funders, non-profit product developers and bio-pharmaceutical industry, non-governmental organisations (NGOs) and civil society groups

Dispel myths that mAbs can't be affordable and that production costs can't be lower by communicating the findings of this report

Global health organisations, academic and public research institutions, manufacturers, non-profit product developers and bio-pharmaceutical industry

Assess the barriers to making mAbs available in public health systems in low- and middle-income countries

Government agencies, health care providers, global health organisations, academic and public research institutions, health technology assessment groups, non-governmental organisations (NGOs) and civil society groups

Conduct studies to model the health and economic impact of introducing mAbs in developing countries

Government agencies, global health organisations, academic and public research institutions, health technology assessment groups

Promote access through global health agendas

Influencers and leaders of global health organisations, including the Bill & Melinda Gates Foundation, Wellcome, Unitaid; policy makers and influencers associated with universal healthcare, non-governmental organisations (NGOs) and civil society groups

Include mAbs in epidemic/pandemic preparedness initiatives as an important complement to vaccines

Government agencies and ministries of health, global health organisations, non-governmental organisations (NGOs) and civil society groups

Convene key opinion leaders from private, public and philanthropic entities to align on access pathways

Wellcome, IAVI, all stakeholders mentioned above

OUTCOMES

- ✔ Advocacy networks established that focus on increasing the availability of mAbs in low- and middle-income countries
- ✔ Key barriers addressed that prohibit broader availability of mAbs in public health systems
- ✔ Value proposition established, using health and economic modeling studies, for the introduction of mAbs in low- and middle- income countries
- ✔ Goals related to mAb development and access included in existing global health agendas (examples include: UN-backed Sustainable Development Goals, Universal Health Coverage, Wellcome Flagship Initiatives and the Coalition for Epidemic Preparedness Innovations)
- ✔ Commitments secured on calls to action for global access to mAbs at a Key Opinion Leader meeting held by Wellcome and IAVI

PART II: POLICY AND REGULATORY

Support broader registration and availability of monoclonal antibodies across the globe

Action > **Develop disease-specific guidelines for mAbs to ensure products are designed with local population needs in mind**

Who's needed > *Non-profit product developers, bio-pharmaceutical industry, manufacturers; global health organisations (including WHO); governments; national regulatory agencies; stringent regulatory authorities*

Harmonise and expand existing policy and regulatory pathways in low- and middle-income countries

Non-profit product developers, bio-pharmaceutical industry, manufacturers; global health organisations (including WHO); government agencies; national regulatory agencies; stringent regulatory authorities; African Medicines Agency; African Vaccine Regulatory Forum

Encourage product developers to engage with the WHO early in the development process to clarify pathways for inclusion in policy guidelines and to enable prequalification.

WHO, non-profit product developers and bio-pharmaceutical industry

Identify barriers to adding mAbs to the WHO's Model List of Essential Medicines or in getting more mAbs prequalified by the WHO

WHO, global health organisations, government agencies, non-profit product developers and bio-pharmaceutical industry

Identify barriers to mAbs being added to national essential medicines lists following their approval by stringent regulatory authorities, their being prequalified or added to the EML

Government agencies, ministries of health, WHO, national regulatory agencies, health technology assessment groups

Expand use of collaborative regulatory initiatives between stringent and national regulatory authorities to address limited regulatory capacity in developing countries

WHO, non-profit product developers and bio-pharmaceutical industry, African Medicines Agency, African Vaccine Regulatory Forum, national regulatory authorities

OUTCOMES

- ✔ More mAbs are registered in more low- and middle-income countries faster and included in public health programmes
- ✔ More mAb products are developed based on individual, local and regional preferences
- ✔ Initiatives including the African Medicines Agency and the African Vaccine Regulatory Forum help address regulatory barriers to mAb licensure in Africa
- ✔ More mAbs are prequalified by the WHO, added to WHO's EML and added to essential medicines list in developing countries
- ✔ Access is expanded to mAbs that are either prequalified or included in essential medicines list

GOAL 2

Make mAbs more affordable in low- and middle-income countries

PART I: INNOVATION

Invest in and deploy innovative technologies to lower monoclonal antibody development costs

Action > **Engage public-private partnerships and funders to drive mAb innovation with an end-to-end perspective**

Who's needed > *Funders, non-profit product developers and bio-pharmaceutical industry, global health organisations, academic and public research institutions*

Develop and refine target product profiles that prioritise affordability and acceptability for low- and middle-income countries at all stages of mAb discovery and development.

Non-profit product developers and bio-pharmaceutical industry, global health organisations, academic and public research institutions, technology companies

Ensure that appropriate technologies (and companion diagnostics if needed) are integrated early into product development and are responsive to the specific diseases, patient populations and communities in which they will be introduced

Non-profit product developers and bio-pharmaceutical industry, technology companies, global health organisations, academic and public research institutions, funders

Develop and apply new technologies and platforms that have the potential to lower costs throughout the production process from antibody isolation to manufacturing to delivery

Funders, non-profit product developers and bio-pharmaceutical industry, manufacturers, academic and public research institutions, technology companies, global health organisations

Apply technological lessons learned from developing and producing lower-priced biosimilars and some lower-priced innovative mAbs to further lower prices of marketed mAbs as well as those in development

Low-cost LMIC manufacturers, biosimilar companies

OUTCOMES

- ✔ Increased and diversified funding available for the research and development of mAbs for global health
- ✔ Proven technologies and platforms are applied to discovery, optimisation and development of pipeline mAbs that can prevent and treat infectious and neglected diseases, including drug-resistant bacterial infections, epidemics such as Ebola and pandemics such as COVID-19
- ✔ Proven technologies and platforms are applied to dramatically lower production and delivery costs of licensed innovative and biosimilar mAb products

Create new business models that enable different market approaches in low-, middle- and high-income countries

Action > **Establish collaborations between public, private and philanthropic entities to expand access to innovative and biosimilar mAbs in low- and middle-income countries**

Who's needed > *Non-profit product developers, bio-pharmaceutical industry, manufacturers; funders; global health organisations; academic and public research institutions*

Expand existing but limited industry-led patient access plans that focus on enhancing access to innovative medicines as well as strengthening health systems, diagnostic capabilities and research capacity in developing countries

Non-profit product developers, bio-pharmaceutical industry, manufacturers; governments global health organisations; funders

Develop or expand global pricing frameworks for mAbs, including the use of second brands, to introduce existing biosimilar and innovative mAbs in low- and middle-income countries

Non-profit product developers, bio-pharmaceutical industry, manufacturers; health technology assessment groups; government agencies

Identify donor-funded procurement agencies that can support broader access to mAbs in developing countries

Global health organisations, funders

Explore alternate manufacturing and supply chains in different regions that enable market differentiation and provision of more affordable mAbs in low- and middle-income countries

Non-profit product developers, bio-pharmaceutical industry, manufacturers; procurement groups; government agencies

Identify creative solutions to manage intellectual property rights related to mAbs that encourage innovation, while also prioritising access to affordable mAb products

Unitaid; Medicines Patent Pool; non-profit product developers, bio-pharmaceutical industry, manufacturers; global health organisations

OUTCOMES

- ✔ Public-private partnerships focused on developing mAbs for infectious/neglected diseases establish comprehensive and innovative plans for global commercialisation of and access to eventual products
- ✔ More companies establish scalable patient access schemes to expand access to existing mAbs
- ✔ More affordable products, including second brands and biosimilars, are introduced in low- and middle-income countries
- ✔ A Gavi-like model of procurement is established for mAbs to enable a lower cost and sustainable supply of antibodies in developing countries
- ✔ Alternate intellectual property agreements that prioritise access are implemented in developing countries

References

1. The Antibody Society. Therapeutic monoclonal antibodies approved or in review in the EU or the US. Accessed 4/2/20 from https://www.antibodysociety.org/resources/approved-antibodies

2. Mulangu S, et al. (2019) A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. New England Journal of Medicine. https://doi.org/10.1056/NEJMoa1910993

3. Maxmen A. (2019) Two Ebola drugs show promise amid ongoing outbreak. Nature 12 August. https://doi.org/10.1038/d41586-019-02442-6

4. EMA press office. First vaccine to protect against Ebola. Accessed 27/10/19 from https://www.ema.europa.eu/en/news/first-vaccine-protect-against-ebola

5. Gaudinski MR, et al. (2018) Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults. PLoS Med 15(1): e1002493. https://doi.org/10.1371/journal.pmed.1002493

6. Sok D, Burton DR. (2018) Recent progress in broadly neutralizing antibodies to HIV. Nat Immunol 19(11): 1179-88. https://doi.org/10.1038/s41590-018-0235-7

7. Urquhart L. (2020) Top companies and drugs by sales in 2019. Nat Rev Drug Discov 19(4): 228. https://doi.org/10.1038/d41573-020-00047-7

8. Pharma Intelligence. Pharma R&D Annual Review 2018 May 16. Accessed from https://pharmaintelligence.informa.com/resources/product-content/sitecore/shell/~/media/informa-shop-window/pharma/files/pdfs/pharma-rd-annual-review-webinar-2018-slides.pdf

9. Kaplon H, Reichert JM. (2019) Antibodies to watch in 2019. MAbs 11(2): 219-38. https://doi.org/10.1080/19420862.2018.1556465

10. Walker LM, Burton DR. (2018) Passive immunotherapy of viral infections: 'super-antibodies' enter the fray. Nat Rev Immunol 18(5): 297-308. https://doi.org/10.1038/nri.2017.148

11. Mukherjee A, et al. (2019) Antibody drug conjugates: Progress, pitfalls, and promises. Hum Antibodies 27(1): 53-62. https://doi.org/10.3233/HAB-180348

12. Labrijn AF, et al. (2019) Bispecific antibodies: a mechanistic review of the pipeline. Nat Rev Drug Discov 18(8): 585-608. https://doi.org/10.1038/s41573-019-0028-1

13. Strohl WR. (2018) Current progress in innovative engineered antibodies. Protein Cell 9(1): 86-120. https://doi.org/10.1007/s13238-017-0457-8

14. Blackstone EA, Joseph PF. (2013) The economics of biosimilars. Am Health Drug Benefits 6(8): 469-78.

15. Kumar A, Nanda A. (2017) Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries. Pharmaceutical Regulatory Affairs: Open Access 06. https://doi.org/10.4172/2167-7689.1000185

16. Moorkens E, et al. (2017) The Market of Biopharmaceutical Medicines: A Snapshot of a Diverse Industrial Landscape. Front Pharmacol 8: 314. https://doi.org/10.3389/fphar.2017.00314

17. Coherent Market Report. (2019) MONOCLONAL ANTIBODIES MARKET. Global Industry Insights, Trends, Outlook, and Opportunity Analysis, 2018–2026.

18. Meher B, et al. (2019) Biosimilars in India; current status and future perspectives. Journal of Pharmacy And Bioallied Sciences 11(1): 12-5. https://doi.org/10.4103/jpbs.Jpbs_167_18

19. CDSCO. List of Approved Drugs in India (from 2009-2019). Accessed 20/8/19 from https://cdsco.gov.in/opencms/opencms/en/Approval_new/Approved-New-Drugs

20. IAVI pipeline analysis. Searched: Clinicaltrials.gov, WHO International Clinical Trials Registry Platform, Dimesions (literature, grants, and clinical trials) database, Pubmed, News sources and grey literature.

21. Biocon. Bicon website from https://www.biocon.com

22. U.S. International Trade Commission. The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Drug Market /EC200705A.pdf. Office of Economics Working Paper from https://www.usitc.gov/publications/332

23. SunPharma. Official website. Accessed 15/9/19 from https://www.sunpharma.com

24. Serum Institute of India. NeuClone Pipeline. Accessed 15/9/19 from https://neuclone.com/serum-institute-of-india

25. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. Accessed 20/8/19 from http://ghdx.healthdata.org/gbd-results-tool

26. Murray CJL, et al. (2018) Population and fertility by age and sex for 195 countries and territories, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 392(10159): 1995-2051. https://doi.org/10.1016/S0140-6736(18)32278-5

27. WHO. WHO Cancer Key Facts. 12 September 2018. Accessed 19/6/19 from https://www.who.int/news-room/fact-sheets/detail/cancer

28. Cancer Alliance Collect South African Voices for Cancer. Breast Cancer and HER2+ Breast Cancer with a Look at Trastuzumab Access in South Africa. August 2018. Accessed 12/8/19 from https://canceralliance.co.za/access-to-medicine/trastuzumab-access

29. Wu Y. Faster import to China for breast cancer drug Herceptin. ChinaDaily. Accessed 15/6/19 from http://www.chinadaily.com.cn/a/201806/13/WS5b20cb18a31001b8257212e7.html

30. MIMS. Drug treatment guidelines. https://www.mims.co.uk/guidelines

31. IBM Micromedex. Red Book. Accessed 15/2/2020 from https://www.micromedexsolutions.com

32. IndiaMart. Online Pharmacy. Accessed 15/2/2020 from https://dir.indiamart.com/impcat/online-pharmacy.html

33. Blackwell K, et al. (2018) The Global Need for a Trastuzumab Biosimilar for Patients With HER2-Positive Breast Cancer. Clin Breast Cancer 18(2): 95-113. https://doi.org/10.1016/j.clbc.2018.01.006

34. Lammers P, et al. (2014) Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. Pharmaceuticals (Basel) 7(9): 943-53. https://doi.org/10.3390/ph7090943

35. Vanderpuye V, et al. (2017) Pilot Survey of Breast Cancer Management in Sub-Saharan Africa. J Glob Oncol 3(3): 194-200. https://doi.org/10.1200/JGO.2016.004945

36. Ferreira CG, et al. (2018) Increasing access to immuno-oncology therapies in Brazil. Journal of Cancer Policy 16: 1-5. https://doi.org/10.1016/j.jcpo.2017.12.004

37. ET Bureau. MSD launches blockbuster cancer drug Keytruda in India The Economic Times 13 September 2017. Accessed 13/8/19 from https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/msd-launches-blockbuster-cancer-drug-keytruda-in-india/articleshow/60487138.cms

38. WHO. The WHO Essential Medicines List (EML): 30th anniversary. Accessed 16/8/19 from https://www.who.int/medicines/events/fs/en

39. Rubbert-Roth A, Finckh A. (2009) Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther 11 Suppl 1: S1. https://doi.org/10.1186/ar2666

40. Underwood G. (2014) Humira biosimilar released in India. PharmFile.

41. Amgen. Amgen 2019 Annual Report. Accessed from http://investors.amgen.com/static-files/d45cb739-9637-4e13-856c-e2fc29571032

42. Samsung Bioepis. Samsung Bioepis expands autoimmune portfolio in the United States with FDA approval of ETICOVO (etanercept-ykro), a biosimilar referencing ENBREL (etanercept). 29 April 2019. Accessed 13/8/19 from https://www.biosimilardevelopment.com/doc/samsung-bioepis-expands-autoimmune-portfolio-in-the-united-states-with-fda-approval-of-eticovo-etanercept-ykro-a-biosimilar-referencing-enbrel-etanercept-0001

43. Pollack A. Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions. New York Times 15 July 2016. Accessed 20/8/19

44. NICE. Preventing recurrence of Clostridium difficile infection: bezlotoxumab. Accessed from https://www.nice.org.uk/advice/es13/chapter/Product-overview

45. NICE. Preventing recurrence of Clostridium difficile infection: bezlotoxumab. Accessed 14/2/20 from https://www.nice.org.uk/advice/es13/chapter/Product-overview

46. Merck. Merck Annual Report 2018. Accessed 16/7/19 from https://www.merck.com/finance/proxy/overview.html

47. Balsells E, et al. (2019) Global burden of Clostridium difficile infections: a systematic review and meta-analysis. J Glob Health 9(1): 010407. https://doi.org/10.7189/jogh.09.010407

48. Bernama. Four-month-old baby with chronic lung disease needs assistance. New Straits Times 27 November 2015. Accessed 20/9/19 from https://www2.nst.com.my/news/2015/11/114214/four-month-old-baby-chronic-lung-disease-needs-assistance

49. Delgado DC. CCSS denied expensive medicine to premature baby with weak health [translation]. 26 June 2015. Accessed 20/8/19.

50. Humphreys G. (2015) Hubs to spread technology and save lives. Bull World Health Organ 93(5): 290-1. https://doi.org/10.2471/BLT.15.020515

51. Yu J, et al. (2019) Respiratory Syncytial Virus Seasonality, Beijing, China, 2007-2015. Emerg Infect Dis 25(6): 1127-35. https://doi.org/10.3201/eid2506.180532

52. AstraZenca. Full-Year 2018 Results. Accessed 12/8/19 from https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2018/PDF/AstraZeneca_AR_2018.pdf

53. Utrecht Centre for Affordable Biotherapeutics. Biosimilar palivizumab. Accessed 12/8/19 from https://www.uu.nl/en/organisation/utrecht-centre-for-affordable-biotherapeutics/projects/biosimilar-palivizumab

54. Zydus Cadila. Zydus to launch novel biologic for rabies, Twinrab. 3 September 2019. Accessed 27/10/19 from https://zyduscadila.com/public/pdf/pressrelease/Zydus%20to%20launch%20novel%20biologic%20for%20rabies_WHO.pdf

55. Access to Medicine Foundation. Access to Medicine Index 2018. November 2018. Accessed 8/8/19 from https://accesstomedicinefoundation.org/media/uploads/downloads/5d25b3dd5f128_5cb9b00e8190a_Access-to-Medicine-Index-2018.pdf

56. WHO. Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 70.12: operative paragraph 2.9 on pricing approaches and their impacts on availability and affordability of medicines for the prevention and treatment of cancer. Accessed 9/9/19 from https://apps.who.int/iris/handle/10665/277190

57. IAVI Registration Analysis. Searched: FDA Drug Approvals, European Medicines Agency Medicines, Agência Nacional de Vigilância Sanitária, Egyptian Drug Authority, Nigerian National Agency for Food and Drug Administration and Control, Indian Central Drugs Standard Control Organisation, Medicines Control Authority of Zimbabwe, South African Medicine Price Registry from https://www.accessdata.fda.gov/scripts/cder/daf/, http://norcb.gov.eg/, https://www.nafdac.gov.ng/, https://cdscoonline.gov.in/CDSCO/Drugs, https://www.ema.europa.eu/en/medicines, http://portal.anvisa.gov.br/en/english, http://www.mcaz.co.zw/, http://www.mpr.gov.za

58. Taneja R, et al. (2018) An Assessment of Global Chemistry, Manufacturing and Controls (CMC) Regulatory Requirements in Low and Middle Income Countries. WHO Drug Information 32(3).

59. WHO. Improving the quality of medical products for universal access. Accessed 16/8/19 from https://www.who.int/medicines/regulation/fact-figures-qual-med/en/

60. Qing XV, Langer E. China Looks Inward and Outward: Investments in US and EU Biopharmaceutical Companies Are on the Rise. 17 May 2019. Accessed 17/8/19 from https://bioprocessintl.com/business/bioregions/china-looks-inward-and-outward-investments-in-us-and-eu-biopharmaceutical-companies-are-on-the-rise/

61. Fogarty International Center. Research needed to treat sickle cell disease in Africa December 2014. Accessed 23/9/19 from https://www.fic.nih.gov/News/GlobalHealthMatters/november-december-2014/Pages/sickle-cell-disease.aspx#charts

62. Novartis. New Novartis medicine Adakveo® (crizanlizumab) approved by FDA to reduce frequency of pain crises in individuals living with sickle cell disease. Accessed 5/2020 from https://www.novartis.com/news/media-releases/new-novartis-medicine-adakveo-crizanlizumab-approved-fda-reduce-frequency-pain-crises-individuals-living-sickle-cell-disease

63. Clarivate Analytics. Clarivate Analytics Launches Cortellis CMC Intelligence to Expand Drug Availability in Low and Middle Income Countries. Accessed 17/8/18 from https://clarivate.com/news/clarivate-analytics-launches-cortellis-cmc-intelligence-to-expand-drug-availability-in-low-and-middle-income-countries/

64. Duenas-Gonzalez A, Gonzalez-Fierro A. (2019) Barriers for Pharmaceutical Innovation With Focus in Cancer Drugs, the Case of Mexico. Therapeutic Innovation & Regulatory Science: 2168479019839015. https://doi.org/10.1177/2168479019839015

65. Vaidyanathan G. India's clinical-trial rules to speed up drug approvals. Nature 03 APRIL 2019. Accessed 20/8/19 from https://www.nature.com/articles/d41586-019-01054-4

66. Clarivate Analytics. Cortellis database search. Accessed 1/7/19.

67. Kahn T. Teva cracks first nod for biosimilar drug. Business Day 24 July 2018. Accessed 2/9/19 from https://www.businesslive.co.za/bd/companies/healthcare/2018-07-24-teva-cracks-first-nod-for-biosimilar-drug/

68. Kanase J, et al. (2013) BIOSIMILAR: AN OVERVIEW. IJPSR 4(6): 2132-44. https://doi.org/10.13040/IJPSR.0975-8232.4(6).2132-44

69. WHO. Accelerated Registration of Prequalified FPPs. Accessed 9/3/19 from https://extranet.who.int/prequal/content/collaborative-registration-faster-registration

70. FDA. President's Emergency Plan for AIDS Relief (PEPFAR). Accessed 7/9/19 from https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar

71. WHO. New FDA-WHO joint pilot to accelerate access to HIV medicines. Accessed 2/2/20 from https://www.who.int/medicines/news/2018/FDA-WHO-joint-pilot-to-accelerate-access-to-HIV-medicines/en/#:~:text=In%20the%20pilot%2C%20called%20the,for%20one%20or%20two%20medicines

72. EMA. Workshop on making Article 58 and other European Medicines Agency outputs more relevant for non-EU regulators 26 April 2017. Accessed 17/8/19 from https://www.ema.europa.eu/en/documents/report/workshop-report-making-article-58-other-european-medicines-agency-outputs-more-relevant-non-eu_en.pdf

73. WHO. Four countries in the African region license vaccine in milestone for Ebola prevention. Accessed 15/3/2020 from https://www.who.int/news-room/detail/14-02-2020-four-countries-in-the-african-region-license-vaccine-in-milestone-for-ebola-prevention

74. Ahonkhai V, et al. (2016) Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. PLOS ONE 11(11): e0166515. https://doi.org/10.1371/journal.pone.0166515

75. WHO. Accelerated Registration of FPPs Approved by SRAs. Accessed 9/9/19 from https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras

76. Zarocostas J. (2018) Health ministers adopt African Medicines Agency treaty. Lancet 391(10137): 2310. https://doi.org/10.1016/s0140-6736(18)31313-8

77. Ndomondo-Sigonda M, et al. (2017) Medicines Regulation in Africa: Current State and Opportunities. Pharmaceut Med 31(6): 383-97. https://doi.org/10.1007/s40290-017-0210-x

78. IFPMA. IFPMA Welcomes Set-Up of New African Medicines Agency. Accessed 19/9/19 from https://www.ifpma.org/resource-centre/ifpma-welcomes-set-up-of-new-african-medicines-agency/

79. Ndomondo-Sigonda M, et al. (2017) Medicines Regulation in Africa: Current State and Opportunities. Pharmaceutical medicine 31(6): 383-97. https://doi.org/10.1007/s40290-017-0210-x

80. WHO. WHO's 4th Product Development for Vaccines Advisory committee (PDVAC) meeting. 21-23 June 2017. Accessed 18/9/19 from https://www.who.int/immunization/research/meetings_workshops/PDVAC_2017_Executive_Summary.pdf?ua=1

81. Sidebottom D, et al. (2018) A systematic review of adherence to oral pre-exposure prophylaxis for HIV—how can we improve uptake and adherence? BMC Infect Dis 18(1): 581. https://doi.org/10.1186/s12879-018-3463-4

82. HAI. Morocco—Medicine prices, availability, affordability and price components. Accessed 15/619 from http://haiweb.org/wp-content/uploads/2015/07/Morocco-Summary-Report-Pricing-Surveys.pdf

83. WHO. Pilot Procedure for Prequalification of Biotherapeutic Products and Similar Biotherapeutic Products. Accessed 26/8/19 from https://www.who.int/medicines/regulation/prequalification/01_Pilot_Prequalification_BTPs_June2018.pdf?ua=1

84. Haque M. (2017) Essential Medicine Utilization and Situation in Selected Ten Developing Countries: A Compendious Audit. J Int Soc Prev Community Dent 7(4): 147-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5558247

85. WHO. National Medicines List/Formulary/Standard Treatment Guidelines. Accessed 2/3/2020 from https://www.who.int/selection_medicines/country_lists/en/

86. Surgey G, et al. (2019) Introducing health technology assessment in Tanzania. Int J Technol Assess Health Care: 1-7. https://doi.org/10.1017/s0266462319000588

87. Tanvejsilp P, et al. (2019) Revisiting Roles of Health Technology Assessment on Drug Policy in Universal Health Coverage in Thailand: Where Are We? And What Is Next? Value Health Reg Issues 18: 78-82. https://doi.org/10.1016/j.vhri.2018.11.004

88. Zhen X, et al. (2018) Health Technology Assessment and Its Use in Drug Policies in China. Value Health Reg Issues 15: 138-48. https://doi.org/10.1016/j.vhri.2018.01.010

89. Pilling D. (2018) African economy: the limits of 'leapfrogging'. Financial Times (12 August).

90. Cazap E, et al. (2016) Structural Barriers to Diagnosis and Treatment of Cancer in Low- and Middle-Income Countries: The Urgent Need for Scaling Up. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(1): 14-9. https://doi.org/10.1200/JCO.2015.61.9189

91. WHO. Global Health Observatory data repository. Accessed 9/4/19 from http://apps.who.int/gho/data/node.main.HWFGRP_0020?lang=en

92. WHO. Medicines Pricing and Financing. Accessed 4/3/2020 from https://www.who.int/medicines/areas/access/en/

93. Roy A. (2019) Biologic Medicines: The Biggest Driver Of Rising Drug Prices. Forbes: Mar 8 2019.

94. Hernandez I, et al. (2018) Pricing of monoclonal antibody therapies: higher if used for cancer? Am J Manag Care 24(2): 109-12.

95. Chhatwal J, et al. (2015) Are high drug prices for hematologic malignancies justified? Cancer 121(19): 3372-9. https://doi.org/10.1002/cncr.29512

96. ANAM. L'Agence Nationale de l'Assurance Maladie. Accessed 15/7/19 from http://www.anam.ma

97. Egyptian Drug Authority. Egyptian Drug Database Search. Accessed 15/7/19 from http://norcb.gov.eg/

98. Mukherjee R. Government makes breast cancer drug 25% cheaper. Times of India 12 May 2016. Accessed 15/7/19 from https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/Government-makes-breast-cancer-drug-25-cheaper/articleshow/52233062.cms

99. Ooko S. Cancer war: What Kenya requires for success. Business Daily 5 February 2019. Accessed 15/7/19 from https://www.businessdailyafrica.com/lifestyle/fitness/Cancer-war--What-Kenya-requires-for-success/4258372-4968436-eybcokz/index.html

100. Pearson SD, et al. (2017) Indication-specific pricing of pharmaceuticals in the US healthcare system. J Comp Eff Res 6(5): 397-404. https://doi.org/10.2217/cer-2017-0018

101. Chu M. Does Celltrion's biosimilar have price edge over Roche's Herceptin? Korea Biomedical Review. Accessed 11/11/19 from http://www.koreabiomed.com/news/articleView.html?idxno=3199

102. WHO. WHO guideline on country pharmaceutical pricing policies. Accessed 15/6/19 from https://www.who.int/medicines/publications/pharm_guide_country_price_policy/en/

103. IQVIA Institute. Global Oncology Trends 2018 Innovation, Expansion and Disruption May 2018. Accessed 15/6/19 from https://www.iqvia.com/institute/reports/global-oncology-trends-2018

104. Generics and Biosimilar Initiative. Domestic biologicals cost less in India. Accessed 15/8/19 from http://www.gabionline.net/Biosimilars/Research/Domestic-biologicals-cost-less-in-India

105. Rémuzat C, et al. (2015) Overview of external reference pricing systems in Europe. Journal of market access & health policy 3: 10.3402/jmahp.v3.27675. https://doi.org/10.3402/jmahp.v3.27675

106. Wang T, et al. (2018) Building Synergy between Regulatory and HTA Agencies beyond Processes and Procedures-Can We Effectively Align the Evidentiary Requirements? A Survey of Stakeholder Perceptions. Value Health 21(6): 707-14. https://doi.org/10.1016/j.jval.2017.11.003

107. Zamora B, et al. (2019) Comparing access to orphan medicinal products in Europe. Orphanet Journal of Rare Diseases 14(1): 95. https://doi.org/10.1186/s13023-019-1078-5

108. Covance. Pricing and Reimbursement in Spain. Accessed 15/4/20 from https://www.covance.com/content/dam/covance/assetLibrary/salessheets/Pricing-Reimbursement-Spain-SSCMA056.pdf

109. Gonçalves FR, et al. (2018) Risk-sharing agreements, present and future. Ecancermedicalscience 12: 823. https://doi.org/10.3332/ecancer.2018.823

110. Ferrario A, Kanavos P. (2013) Managed entry agreements for pharmaceuticals: the European experience. LSE Research Online June.

111. European Commission. Mapping of HTA national organisations, programmes and processes in EU and Norway. Accessed 18/11/19 from https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/2018_mapping_npc_en.pdf

112. Kido K, et al. (2019) Health Technology Assessment in Japan: A Pharmaceutical Industry Perspective. Ther Innov Regul Sci 53(4): 472-80. https://doi.org/10.1177/2168479018791136

113. Roche. Access to Healthcare. Accessed 21/9/19 from https://www.roche.com/sustainability/access-to-healthcare.htm

114. Dolgin E. (2018) Bringing down the cost of cancer treatment. Nature 555(7695): S26-S9. https://doi.org/10.1038/d41586-018-02483-3

115. Ramrayka L. A pathway to hope. Accessed 15/4/19 from https://www.roche.com/sustainability/access-to-healthcare/cancer-care-partnerships-kenya.htm

116. Cost control: drug pricing policies around the world. Pharmaceutical Techonology 12 February 2018. Accessed 15/6/19 from https://www.pharmaceutical-technology.com/features/cost-control-drug-pricing-policies-around-world/

117. Trastuzumab (Herceptin) Market in China 2018-2022: Market Share, Major Manufacturers and Prospects BusinessWire. Accessed 15/6/19 from https://www.businesswire.com/news/home/20180702005434/en/Trastuzumab-Herceptin-Market-China-2018-2022-Market-Share

118. Alka A. Emcure to make, market Roche products. The Hindu BusinessLine 1 September 2012. Accessed 10/11/19 from https://www.thehindubusinessline.com/companies/emcure-to-make-market-roche-products/article20497435.ece1

119. Lemgruber A. Pharmacoeconomics and the Decision-making Process: The Brazilian Experience. International Society for Pharmacoeconomics and Outcomes Research. Segunda Conferencia de América Latina, Rio de Janeiro, Brasil.

120. Moraes EL, et al. (2016) Compras federais de antineoplásicos no Brasil: análise do mesilato de imatinibe, trastuzumabe e L-asparaginase, 2004-2013. Physis: Revista de Saúde Coletiva 26: 1357-82.

121. DiMasi JA, et al. (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics 47: 20-33. https://doi.org/https://doi.org/10.1016/j.jhealeco.2016.01.012

122. Kesselheim AS, et al. (2016) The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. JAMA 316(8): 858-71. https://doi.org/10.1001/jama.2016.11237

123. Leviten M. Democratizing antibodies. Biocentury Innovations 1 September 2016. Accessed 14/9/19 from https://www.biocentury.com

124. Griffin MP, et al. (2017) Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. Antimicrob Agents Chemother 61(3). https://doi.org/10.1128/AAC.01714-16

125. Mason DM, et al. (2018) High-throughput antibody engineering in mammalian cells by CRISPR/Cas9-mediated homology-directed mutagenesis. Nucleic Acids Res 46(14): 7436-49. https://doi.org/10.1093/nar/gky550

126. Just Biotherapeutics. Gates Foundation Invests in Just Biotherapeutics. Accessed 14/8/19 from http://www.justbiotherapeutics.com/news

127. Shukla AA, et al. (2017) Evolving trends in mAb production processes. Bioengineering & translational medicine 2(1): 58-69. https://doi.org/10.1002/btm2.10061

128. Walther J, et al. (2015) The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. J Biotechnol 213: 3-12. https://doi.org/10.1016/j.jbiotec.2015.05.010

129. Gjoka X, et al. Platform for Integrated Continuous Bioprocessing. BioPharm International 1 July 2017. Accessed 14/9/19 from http://www.biopharminternational.com/platform-integrated-continuous-bioprocessing

130. Jacquemart R, et al. (2016) A Single-use Strategy to Enable Manufacturing of Affordable Biologics. Computational and Structural Biotechnology Journal 14: 309-18. https://doi.org/https://doi.org/10.1016/j.csbj.2016.06.007

131. Qing X, Yang LC. Demand for Capacity Drives China's Biomanufacturing Expansion. BioPrecess International 20 June 2018. Accessed 15/7/19 from https://bioprocessintl.com/business/bioregions/demand-for-capacity-drives-chinas-biomanufacturing-expansion/

132. WuXi Biologics. Capacity and Capabilities. Accessed 7/9/19 from https://www.wuxibiologics.com/

133. ET Bureau. Serum Institute invests Rs 4,000 crore towards new plant. The Economic Times 9 September 2019. Accessed 27/9/19 from https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/serum-institute-invests-rs-4000-crore-towards-new-plant/articleshow/71049123.cms

134. Robinson M-P, et al. (2015) Efficient expression of full-length antibodies in the cytoplasm of engineered bacteria. Nature Communications 6: 8072. https://doi.org/10.1038/ncomms9072, https://www.nature.com/articles/ncomms9072#supplementary-information

135. Sahin U, et al. (2014) mRNA-based therapeutics — developing a new class of drugs. Nature Reviews Drug Discovery 13: 759. https://doi.org/10.1038/nrd4278

136. Moldovan Loomis C, et al. (2019) Pharmacologic Characterization of ALD1910, a Potent Humanized Monoclonal Antibody against the Pituitary Adenylate Cyclase-Activating Peptide. J Pharmacol Exp Ther 369(1): 26-36. https://doi.org/10.1124/jpet.118.253443

137. (2014) Pichia pastoris Revisited. Genetic Engineering & Biotechnology News 34(11): 30-1. https://doi.org/10.1089/gen.34.11.13

138. Mapp Biopharmaceutical. LeafBio Announces Conclusion of ZMapp™ Clinical Trial. 23 February 2016. Accessed 13/9/19 from https://mappbio.com/leafbio-announces-conclusion-of-zmapp-clinical-trial/

139. Moussavou G, et al. (2015) Production of Monoclonal Antibodies in Plants for Cancer Immunotherapy. BioMed Research International 2015: 9. https://doi.org/10.1155/2015/306164

140. Donini M,Marusic C. (2019) Current state-of-the-art in plant-based antibody production systems. Biotechnol Lett 41(3): 335-46. https://doi.org/10.1007/s10529-019-02651-z

141. Dyadic International. Dyadic and Serum Institute of India to Develop and Manufacture Globally Affordable and Accessible Antibody Products and Vaccines 8 May 2019. Accessed 14/8/19 from https://www.bloomberg.com/press-releases/2019-05-08/dyadic-and-serum-institute-of-india-to-develop-and-manufacture-globally-affordable-and-accessible-antibody-products-an

142. Zhang R, et al. (2018) A novel glycosylated anti-CD20 monoclonal antibody from transgenic cattle. Scientific Reports 8(1): 13208. https://doi.org/10.1038/s41598-018-31417-2

143. Yin G, et al. (2012) Aglycosylated antibodies and antibody fragments produced in a scalable in vitro transcription-translation system. mAbs 4(2): 217-25. https://doi.org/10.4161/mabs.4.2.19202

144. Vanier G, et al. (2015) Biochemical Characterization of Human Anti-Hepatitis B Monoclonal Antibody Produced in the Microalgae Phaeodactylum tricornutum. PLoS One 10(10): e0139282. https://doi.org/10.1371/journal.pone.0139282

145. Yusibov V, et al. (2016) Antibody Production in Plants and Green Algae. Annual Review of Plant Biology 67(1): 669-701. https://doi.org/10.1146/annurev-arplant-043015-111812

146. Dyo YM,Purton S. (2018) The algal chloroplast as a synthetic biology platform for production of therapeutic proteins. Microbiology 164(2): 113-21. https://doi.org/10.1099/mic.0.000599

147. Taunt HN, et al. (2018) Green biologics: The algal chloroplast as a platform for making biopharmaceuticals. Bioengineered 9(1): 48-54. https://doi.org/10.1080/21655979.2017.1377867

148. Palmberger D, et al. (2011) Insect cells for antibody production: evaluation of an efficient alternative. J Biotechnol 153(3-4): 160-6. https://doi.org/10.1016/j.jbiotec.2011.02.009

149. Wang L, et al. (2012) High yield of human monoclonal antibody produced by stably transfected Drosophila schneider 2 cells in perfusion culture using wave bioreactor. Mol Biotechnol 52(2): 170-9. https://doi.org/10.1007/s12033-011-9484-5

150. Priddy FH, et al. (2019) Adeno-associated virus vectored immunoprophylaxis to prevent HIV in healthy adults: a phase 1 randomised controlled trial. Lancet HIV 6(4): e230-e9. https://doi.org/10.1016/s2352-3018(19)30003-7

151. Egashira Y, et al. (2018) Characterization of glycoengineered anti-HER2 monoclonal antibodies produced by using a silkworm-baculovirus expression system. J Biochem 163(6): 481-8. https://doi.org/10.1093/jb/mvy021

152. Stadler CR, et al. (2017) Elimination of large tumors in mice by mRNA-encoded bispecific antibodies. Nat Med 23(7): 815-7. https://doi.org/10.1038/nm.4356

153. Thran M, et al. (2017) mRNA mediates passive vaccination against infectious agents, toxins, and tumors. EMBO Mol Med 9(10): 1434-47. https://doi.org/10.15252/emmm.201707678

154. Perales-Puchalt A, et al. (2019) DNA-encoded bispecific T cell engagers and antibodies present long-term antitumor activity. JCI Insight 4(8). https://doi.org/10.1172/jci.insight.126086

155. Pardi N, et al. (2017) Administration of nucleoside-modified mRNA encoding broadly neutralizing antibody protects humanized mice from HIV-1 challenge. Nat Commun 8: 14630. https://doi.org/10.1038/ncomms14630

156. Tiwari PM, et al. (2018) Engineered mRNA-expressed antibodies prevent respiratory syncytial virus infection. Nat Commun 9(1): 3999. https://doi.org/10.1038/s41467-018-06508-3

157. Patel A, et al. (2018) In Vivo Delivery of Synthetic Human DNA-Encoded Monoclonal Antibodies Protect against Ebolavirus Infection in a Mouse Model. Cell Rep 25(7): 1982-93.e4. https://doi.org/10.1016/j.celrep.2018.10.062

158. Flingai S, et al. (2015) Protection against dengue disease by synthetic nucleic acid antibody prophylaxis/immunotherapy. Sci Rep 5: 12616. https://doi.org/10.1038/srep12616

159. Wise MC, et al. (2019) In vivo delivery of synthetic DNA-encoded antibodies induces broad HIV-1-neutralizing activity. J Clin Invest. https://doi.org/10.1172/JCI132779

160. Elliott STC, et al. (2017) DMAb inoculation of synthetic cross reactive antibodies protects against lethal influenza A and B infections. NPJ Vaccines 2: 18. https://doi.org/10.1038/s41541-017-0020-x

161. Patel A, et al. (2017) An engineered bispecific DNA-encoded IgG antibody protects against Pseudomonas aeruginosa in a pneumonia challenge model. Nat Commun 8(1): 637. https://doi.org/10.1038/s41467-017-00576-7

162. Andrew Lloyd & Associates. Univercells granted €2.4M ($2.9M) to develop antibody production platform 23 January 2018. Accessed 14/8/19 from http://www.ala.com/univercells-granted-e2-4m-2-9m-to-develop-antibody-production-platform

163. Leviten M. Benchtop manufacturing gets smaller. Biocentury 16 November 2018. Accessed 14/9/19 from https://www.biocentury.com

164. Olsen J, et al. (2018) Costs of subcutaneous and intravenous administration of trastuzumab for patients with HER2-positive breast cancer. J Comp Eff Res 7(5): 411-9. https://doi.org/10.2217/cer-2017-0048

165. Viola M, et al. (2018) Subcutaneous delivery of monoclonal antibodies: How do we get there? Journal of Controlled Release 286: 301-14. https://doi.org/10.1016/j.jconrel.2018.08.001

166. Persson MA, et al. (1986) Immunoglobulin G (IgG) and IgA subclass pattern of human antibodies to Shigella flexneri and Salmonella serogroup B and D lipopolysaccharide O antigens. Infect Immun 52(3): 834-9.

167. Giuntini S, et al. (2018) Identification and Characterization of Human Monoclonal Antibodies for Immunoprophylaxis against Enterotoxigenic Escherichia coli Infection. Infect Immun 86(8). https://doi.org/10.1128/iai.00355-18

168. de Sousa-Pereira P. (2019) IgA: Structure, Function, and Developability. Antibodies 8(4): 57. https://doi.org/10.3390/antib8040057

169. Crowe JS, et al. (2018) Preclinical Development of a Novel, Orally-Administered Anti-Tumour Necrosis Factor Domain Antibody for the Treatment of Inflammatory Bowel Disease. Sci Rep 8(1): 4941. https://doi.org/10.1038/s41598-018-23277-7

170. Crowe JS, et al. (2019) Oral delivery of the anti-tumor necrosis factor α domain antibody, V565, results in high intestinal and fecal concentrations with minimal systemic exposure in cynomolgus monkeys. Drug Dev Ind Pharm 45(3): 387-94. https://doi.org/10.108%3639045.2018.1542708

171. Lumen Bioscience. Lumen Wins Triple Funding Boost to Advance Development of Low-Cost Therapeutics for Newborns and Infants in Developing Countries. Accessed 24/5/20 from https://www.lumen.bio/gates-expansion

172. XBiotech. C. DIFFICILE. Accessed 25/5/20 from http://www.xbiotech.com/

173. Tiziana. Foralumab. Accessed 25/5/20 from https://www.tizianalifesciences.com/our-drugs/foralumab/

174. Markarian J. Blow-fill-seal Technology Advances in Aseptic Filling Applications. PharmTech. Accessed 14/9/19 from http://www.pharmtech.com/blow-fill-seal-technology-advances-aseptic-filling-applications

175. Makwana S, et al. (2011) Prefilled syringes: An innovation in parenteral packaging. Int J Pharm Investig 1(4): 200-6. https://doi.org/10.4103/2230-973x.93004

176. Roche. FDA approves Herceptin Hylecta for subcutaneous injection in certain HER2-positive breast cancers. 28 February 2019. Accessed 9/9/19 from https://www.roche.com/media/releases/med-cor-2019-02-28.htm

177. Repatha. (2016) In brief: Repatha Pushtronex– a new evolocumab injection device. Med Lett Drugs Ther 58(1503): 120.

178. Enable Injections. Technology. Accessed 9/9/19 from https://enableinjections.com/technology/enfuse-on-body-infusor/

179. Numab. NTARCIA AND NUMAB SIGN MULTI-ASSET COLLABORATION TO DEVELOP ONCEYEARLY THERAPIES IN DIABETES, OBESITY, AND AUTOIMMUNE INDICATIONS. 19 March 2015. Accessed 15/9/19 from http://numab.com/wp-content/uploads/2016/07/150319_PRP_Intarcia-Numab-collaboration_final.pdf

180. Courtenay AJ, et al. (2018) Microneedle-Mediated Transdermal Delivery of Bevacizumab. Mol Pharm 15(8): 3545-56. https://doi.org/10.1021/acs.molpharmaceut.8b00544

181. Li G, et al. (2009) In vitro transdermal delivery of therapeutic antibodies using maltose microneedles. International Journal of Pharmaceutics 368(1): 109-15. https://doi.org/https://doi.org/10.1016/j.ijpharm.2008.10.008

182. Yang J, et al. (2019) Recent advances of microneedles for biomedical applications: drug delivery and beyond. Acta Pharmaceutica Sinica B 9(3): 469-83. https://doi.org/https://doi.org/10.1016/j.apsb.2019.03.007

183. Portal Instruments. Takeda and Portal Instruments Announce Collaboration to Develop Needle-Free Drug Delivery Device. 7 November 2017. Accessed 10/9/19 from https://www.portalinstruments.com/takeda-portal-instruments-collaboration/

184. Dong J, Mirza Z. (2016) Supporting the production of pharmaceuticals in Africa. Bulletin of the World Health Organization 94: 71-2.

185. Doua JY, Geertruyden J-PV. (2014) Registering medicines for low-income countries: how suitable are the stringent review procedures of the World Health Organisation, the US Food and Drug Administration and the European Medicines Agency? Tropical Medicine & International Health 19(1): 23-36. https://doi.org/10.1111/tmi.12201

186. Baaj A, et al. (2017) Manufacturing Strategy for Diverse Biologic Pipelines of the Future. Tufts Center for the Study of Drug Development Report October.

187. Frost & Sullivan. India's Excellent Standing in Biotechnology Drives Rapid Growth Opportunities. Frost & Sullivan Report March 2017.

188. mAbxience. Biosimilar Medicines. Accessed 17/8/19 from https://www.mabxience.com/

189. PlantForm. Construction to start on new facility for biopharmaceutical innovation and pilot manufacturing in Brazil. 18 June 2018. Accessed 13/8/19 from https://www.plantformcorp.com/file.aspx?id=f56d71c2-3fbb-4ace-a276-361320e2a646

190. Instituto Butantan. Instituto Butantan website. Accessed 13/8/19 from http://butantan.gov.br/instituto-butantan/main-products

191. NNE. Single-use technology for fast capacity expansion. Accessed 7/9/19 from https://www.nne.com/projects/

192. Boehringer Ingelheim. Boehringer Ingelheim Biopharmaceuticals China expands commercial manufacturing capacities. 17 January 2019. Accessed 6/9/19 from https://www.boehringer-ingelheim.com/press-release/capacityexpansionoasis

193. WuXi Biologics. WuXi Biologics and Pall Corporation Establish Joint Continuous Bioprocess Laboratory. 2 Novermber 2017. Accessed 6/9/19 from https://www.prnewswire.com/news-releases/wuxi-biologics-and-pall-corporation-establish-joint-continuous-bioprocess-laboratory-300549125.html

194. HJB. MabSpace Biosciences Merged with HJB to Form Transcenta Holding, a Fully Integrated Leading Global Biotherapeutics Company. 1 January 2019. Accessed 6/9/19 from https://www.prnewswire.com/news-releases/hjb-merges-with-mabspace-biosciences-to-form-transcenta-holding-a-fully-integrated-leading-global-biotherapeutics-company-300771676.html

195. Stanton D. Biocon investing $200m into second MAb plant in India. Bioprocess International 30 October 2018. Accessed 15/7/19 from https://bioprocessintl.com/bioprocess-insider/facilities-capacity/biocon-investing-200m-into-second-mab-plant-in-india/

196. Cipla. Manufacturing. Accessed 6/9/19

197. Fujifilm. Fujifilm Corporation Announces the Introduction of a Novel, Fully Integrated Continuous Production System for the Manufacture of Biopharmaceuticals. 5 June 2019. Accessed 6/9/19 from https://www.prnewswire.com/news-releases/fujifilm-corporation-announces-the-introduction-of-a-novel-fully-integrated-continuous-production-system-for-the-manufacture-of-biopharmaceuticals-300862248.html

198. Staton D. Lonza expands in Asia. Biopharma Reporter 29 June 2017. Accessed 6/9/19 from https://www.biopharma-reporter.com/Article/2017/06/30/Lonza-adds-disposable-and-cell-gene-therapy-capabilities-in-Asia

199. Sothey F. WuXi Biologicas expands. Biopharma Reporter 23 May 2018. Accessed 6/9/19 from https://www.biopharma-reporter.com/Article/2018/05/23/WuXi-Biologics-expands-manufacturing-to-Singapore-with-60m-facility

200. Ryan T. Plant-based Protein Expression for Rapid, Green Bioprocessing. 24 May 2019. Accessed 13/8/19 from https://www.pharmasalmanac.com/articles/plant-based-protein-expression-for-rapid-green-bioprocessing

201. Cipla. Cipla to launch South Africa's first biotech manufacturing facility. 8 July 2016. Accessed 13/8/19 from https://www.cipla.co.za/cipla-news/cipla-launch-south-africas-first-biotech-manufacturing-facility/

202. Medicines Patent Pool. Exploring the expansion of the Medicines Patent Pool's mandate to patented essential medicines. Accessed 7/9/19 from https://medicinespatentpool.org/news-publications-post/exploring-the-expansion-of-the-medicines-patent-pools-mandate-to-patented-essential-medicines-a-feasibility-study-of-the-public-health-needs-and-potential-impact/exploring-the-expansion-of-the-medicines-patent-pools-mandate-to-patented-essential-medicines

203. Beall RF, et al. (2015) Compulsory licensing often did not produce lower prices for antiretrovirals compared to international procurement. Health Aff (Millwood) 34(3): 493-501. https://doi.org/10.1377/hlthaff.2014.0658

204. Son KB, Lee TJ. (2018) Compulsory licensing of pharmaceuticals reconsidered: Current situation and implications for access to medicines. Glob Public Health 13(10): 1430-40. https://doi.org/10.1080/17441692.2017.1407811

205. Wellcome Trust. Achieving Equitable Access to Healthcare Interventions. Accessed 12/3/20 from https://wellcome.ac.uk/sites/default/files/access-to-healthcare-interventions.pdf

206. G FINDER. FUNDING BY DISEASE. Accessed 9/9/19 from https://www.policycuresresearch.org/wp-content/uploads/2019/01/Y11_G-FINDER_Funding_by_disease.pdf

207. Chapman N, et al. (2017) Neglected disease research and development: Reflecting on a decade of global investment. G Finder Report.

208. G-FINDER. G-FINDER reports, 2013 – 2018 Accessed 20/8/19 from https://gfinder.policycuresresearch.org/

209. CARB-X. Combating Antibotic Resistant Bacteria. Accessed 7/9/19 from https://carb-x.org

210. Visterra. Visterra Awarded CARB-X Contract to Advance Development of VIS705. 30 March 2017. Accessed 23/9/19 from http://www.visterrainc.com/wp-content/uploads/2018/1½017-0330-Visterra-CARB-X.pdf

211. CARB-X. CARB-X Funds BB100 to Develop a Unique Monoclonal Antibody to Prevent and Treat Hyper-Virulent Multi-Drug-Resistant E. Coli Infections. Accessed 25/9/19 from https://carb-x.org/carb-x-news/carb-x-funds-bb100-to-develop-a-unique-monoclonal-antibody-to-prevent-and-treat-hyper-virulent-multi-drug-resistant-e-coli-infections

212. Initiative IM. AMR Accelerator Programme. Accessed 4/9/19 from https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/future-topics/IndicativeText_AMRAcceleratorIntro.pdf

213. COMBACTE. Effort to Prevent Nosocomial Pneumonia caused by Pseudomonas aeruginosa in Mechanically ventilated Subjects. Accessed 7/9/19 from https://www.combacte.com/trials/evade

214. REPAIR Impact Fund. Introduction. Accessed 7/9/19 from https://www.repair-impact-fund.com

215. NIH. Antimicrobial Resistance Diagnostic Challenge. 29 January 2019. Accessed 7/9/19 from https://dpcpsi.nih.gov/AMRChallenge

216. LifeArc. Kymab and LifeArc enter strategic partnership to discover new medicines using Kymab's IntelliSelect® technologies. Accessed 15/11/19 from https://www.lifearc.org/kymab-lifearc-enter-strategic-partnership

217. Department of Health and Social Care. Development of new antibiotics encouraged with new pharmaceutical payment system. 9 July 2019. Accessed 7/9/19 from https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system

218. IAVI. Global Funding & Support. Accessed 8/9/19 from https://www.iavi.org/about/global-funding-support

219. IAVI. IAVI and Serum Institute of India to Develop and Manufacture Globally Affordable and Accessible Antibody Products for HIV. 22 October 2018 from https://www.iavi.org/newsroom/press-releases/2018/iavi-and-serum-institute-of-india-to-develop-and-manufacture-globally-affordable-and-accessible-antibody-products-for-hiv

220. IAVI. IAVI and Liverpool School of Tropical Medicine to Partner in Snakebite Consortium. 16 May 2019. Accessed 28/10/10 from https://www.iavi.org/newsroom/press-releases/2019/iavi-lstm-snakebite-announcement

221. Rogers TF, et al. (2020) Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science. https://doi.org/10.1126/science.abc7520

222. WHO. Noncommunicable Diseases Progress Monitor 2017. Accessed 15/6/19 from https://ncdalliance.org/why-ncds

223. Roche. Helping people receive cancer treatment in China. Accessed 15/6/19 from https://www.roche.com/sustainability/access-to-healthcare/ath_china_pap.htm

224. Takeda. Takeda R&D access to medicines summary report. Accessed 20/8/19 from https://www.takeda.com/siteassets/system/what-we-do/access-to-medicines/progressreport_2018.pdf

225. Access to Medicines Foundation. Are pharmaceutical companies making progress when it comes to global health? May 2019. Accessed 20/8/19 from https://accesstomedicinefoundation.org/publications/are-pharmaceutical-companies-making-progress-when-it-comes-to-global-health

226. WHO. WHO Price Report. Accessed 16/6/19 from https://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/WHO_Price_Report_2016.pdf

227. GAVI. Donor Profiles. Accessed 15/5/19 from https://www.gavi.org/investing/funding/donor-profiles

228. WHO. Report: WHO meeting on monoclonal antibodiesagainst rabies and evaluation of mechanisms to improve access to other blood-derived immunoglobulins. 18 July 2017. Accessed 15/9/19 from https://www.who.int/immunization/research/meetings_workshops/Report_mAbs_access_immunoglobulins_18July2017.pdf

229. Shi T, et al. (2017) Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. The Lancet 390(10098): 946-58. https://doi.org/10.1016/s0140-6736(17)30938-8

230. WHO. WHO prequalifies first biosimilar medicine to increase worldwide access to life-saving breast cancer treatment. 18 December 2019. Accessed 20/12/2019 from https://www.who.int/news-room/detail/18-12-2019-who-prequalifies-first-biosimilar-medicine-to-increase-worldwide-access-to-life-saving-breast-cancer-treatment

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